DEATH AND DYING IN THE INTENSIVE CARE UNIT

Practical issues and ethical dilemmas from a Dutch perspective

J.L. Epker, 2015

Cover:

The old and new railway bridge
over the Hollands Diep at Moerdijk
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Acherontia Atropos or Death Moth

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DEATH AND DYING IN THE INTENSIVE CARE UNIT; PRACTICAL ISSUES AND ETHICAL DILEMMAS FROM A DUTCH PERSPECTIVE

STERVEN EN DE DOOD OP DE INTENSIVE CARE; PRAKTISCHE ZAKEN EN ETHISCHE DILEMMA'S VANUIT EEN NEDERLANDS GEZICHTSPUNT

Thesis

to obtain the degree of Doctor from the
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L' chaim!

CONTENT OF THE THESIS

1

"There are, aren't there, only three things that we can do about death: to desire it, to fear it, or to ignore it."

C.S. Lewis,
20th century writer,
poet, medievalist
and lay theologian

GENERAL INTRODUCTION

Over the past decades the developments in intensive care medicine have been immense. On-going innovations in the field of ventilation, antibiotic therapy, hemodynamic monitoring and imaging of the microcirculation have changed the world of intensive care dramatically.[1] We come, for example, from the iron lung, invented in the '20's of the last century, and used and improved during the great polio outbreaks in the '50's [2] and nowadays we can use a neurally adjusted ventilation assist mode in portable positive pressure ventilators as if it has always been that way.[3] And even that is not the end, portable Extra Corporal Membrane Oxygenators (ECMO) give the possibility to start mobilisation already in the ICU even without any ventilation present in patients with severe respiratory insufficiency.[4] Apparently all these developments have not been in vain; in the last 20 to 30 years the mortality rates on intensive care units (ICUs) in the Western world have decreased significantly.[5,6]

However, despite all these efforts and the money invested, mortality is still high for ICU patients. Unfortunately still 15 to 20 percent of all patients will eventually die in the intensive care unit [7,8], moreover a percentage of even up to 65 percent in some patient categories will subsequently die in the year after ICU discharge. Even when patients survive in the end, survival comes at a great cost, both literally and figuratively. Literally because the large part of the economic burden of, for example, severe sepsis occurs after discharge. Lost productivity and other indirect

medical costs following hospitalization account for the majority (70 percent) of the economic burden of sepsis.[9] Figuratively, because morbidity after ICU survival is high and leads inevitably to a significant loss of quality of life.[10]

The foremost reason why patients die in the ICU nowadays is the decision of the medical team to withdraw some or even all life-sustaining therapies. In the Netherlands about 85 percent of patients who die in the ICU, die after a decision to withdraw life-sustaining measures and this percentage is not very different from the number in other Northern European countries.[8,11] Most withdrawal decisions are predominately motivated by the absence of (a perspective on) success of the therapy or the occurrence of a situation that is so complicated that there will be no "life" for the patient outside the protective and supportive environment of an ICU. In rare cases it is the patient him/herself that asks for termination of life-support in such a situation.[12,13] The last two scenarios are mostly quite easy to identify, the first however is often far less easy to define. Disease severity scores and organ failure assessment scores are helpful in characterising patients groups with bad outcome, but inevitably they fail to predict definite outcome on an individual level.[14] This is especially true for young patients with ostensible severe neurological damage, because predicting the rate of recovery and the eventual outcome in this specific group is extremely difficult if not impossible. Withdrawing life-sustaining measures too early in this specific patient group automatically creates an unwanted self-fulfilling prophecy.
Even in case of severely ill ICU patients for whom no further treatment is available, so that death will be the inevitable final outcome, it is often unclear when exactly the patient will die. This uncertainty about the time path till death is a well-recognized stress factor for families of a dying ICU patient. Therefore it is important to be able to give families reliable information about the factors influencing the time till death of their loved one. Moreover it is observed that this kind of information reduces stress and hence avoids unnecessary tension around the deathbed.[15]

The need for clarity about the moment of death, or in other cases the chance of survival of the patient when potential treatment is available, is certainly not specific to our time and culture. There seems to be an inclination to think that the

need for knowledge for predicting prognosis or the time of death is something specific for our era and Western culture. Some believe that it maybe correlated with the development of modern medicine and the decreasing influence of "the church" or religion in general. However, the question "will he live or will he die soon?" was equally relevant from the overt religious medieval times to deep into the superstitious nineteenth century as is well documented by J. Devlin for French peasants in Normandy (France). Doctors, if available at all, were not capable of giving adequate care let alone predicting prognosis.[16] The extensive existing religious framework of saints did cover all kind of problems and diseases, but none of them was considered adequate for settling the problem of distinction between rapid recovery versus a certain and quick death. Therefore, without the consent of the Church, a new saint was constructed or "invented", the so-called "Va et Vient". This "saint" was supposed to be able to predict or even cause a rapid death or a literally miraculously fast recovery. Notably, a protracted sickbed was also in these days definitely not the desired outcome. In this perspective it is important to realize that in the past centuries the predictive power of the answer itself, recovery or death, was sometimes even more important than the actual outcome. Nowadays, with the availability of high standards of medical care as described above, this is certainly not the case anymore. Most families in the era of modern medicine prefer a good outcome over the right prediction of outcome. So the questions remain the same over time but the desired answers have changed, 'o tempora o mores'!

The articles in this thesis are written from the perspective of the intensive care unit, so all patients studied had already past the ICU admission criteria. Therefore all patients were in the ICU with a perspective of potential benefit. The questions when and whether or not a patient should be admitted to the ICU are not a part of this thesis.

When a patient dies in the intensive care unit there are generally four treatment regiments that can precede the death of the patient.

1. *The patient dies under a full treatment regiment, despite the intense efforts of the ICU team. The patient dies from the underlying disease or condition.*
2. *The patient is admitted to the ICU, but some pre-defined treatment schemes like CPR or renal replacement therapy will not be initiated. When one of the excluded organ systems fails the patient will die subsequently from one or more organ failure.*
3. *The patient is admitted to the ICU and is given full treatment. Unfortunately the treatment fails to improve the patient's condition and is therefore considered disproportionate. Then the life-sustaining measures, that were so hopefully initiated, are withdrawn. The patient will die very quickly thereafter in most cases.*
4. *The patient did have an advance directive, which unfortunately became available only after ICU treatment was initiated. ICU treatment is based on that directive withdrawn. The patient dies subsequently thereafter.*

As already mentioned above, nowadays in many Northern-European countries (including the Netherlands), most patients that die in the ICU follow the path as depicted in scheme 3 in numbers up to 85 percent.
Since the percentage of death and withdrawal of life-sustaining measures in the ICU is so very high, one would expect there to be an extensive amount of literature concerning intensive care related end-of-life issues. Surprisingly this is not the case; on the contrary, there is relatively little literature on ethics and end of-life issues when compared with the size of the patient group and the vast amount of literature about other ICU topics. When the idea for this thesis was born, there were, for example, neither articles available about the practise of withdrawal of treatment on Dutch intensive care units, nor any articles about the effect of opioids and sedatives in relation to time till death based on prospective data anyware in the literature.
Moreover, an analysis of all the published abstracts of the past congresses of the European Society of Critical Care over the period 2008-2013, showed that not more than 1.3% of the research output in these years was dedicated to end-of-life related issues.[17]
So if end-of-life care in the ICU and the ethical issues involved are a part of intensive care medicine in general, and if one believes that intensive care medicine should be evidence based, then we certainly lack a lot of reliable evidence for good end-of-life care. How can we say that we take good care of our dying patients if we don't even know exactly how we care?

For this thesis there were five main questions to be answered:

1. *What is the general incidence of treatment withdrawal in academic and non-academic ICU's and are there differences in incidence of withdrawal between the different patient groups and what could be the implication of differences?*

2. *What is the actual amount of opioids and sedatives used during treatment withdrawal and do we use more (because of a presumed liberal end-of-life attitude) in the Netherlands than in other countries under the same circumstances?*
3. *What factors do influence the time till death after withdrawal of life-sustaining measures?*
4. *Are the patients in whom life-sustaining measures are withdrawn comfortable and well sedated; is the national protocol for end-of-life care on the ICU introduced in 2007 efficient and effective?*
5. *What are the different ethical dilemmas we can encounter when we are dealing with death and dying on the ICU and how should we cope with them?*

SCOPE AND OUTLINE OF THE THESIS

The main content of this thesis is divided into two parts. In the first part (section I) the results of the studies that describe and analyze the current situation in relation to end-of-life practices and the use of opioids and sedatives in the Netherlands, are presented. This section includes also an editorial on the use of opioids and sedatives in the absence of symptoms.

In the second part (section II) three different specific ethical dilemmas that were encountered in the daily practice during the past four years are presented and discussed. These two sections are followed by a commentary that summarizes and discusses the main findings.

SECTION I

In **chapter 2** the results of a one-year retrospective study analyzing the differences in withdrawal rates between the different patients groups on the intensive care of the Erasmus MC, in whom life-sustaining measures were withdrawn, are presented. Specific attention in this chapter is paid to the meaning and implications of the discovered differences for the daily practice and the near future.

Chapter 3 presents the retrospective analysis of dosages of opioids and sedatives, the time span between the withdrawing of the two principal life sustaining measures (ventilation and vaso-pressive medication) and the time till death from a patient cohort derived from a half year observation time on the main ICU of the Erasmus MC.

In **chapter 3-1** we respond to a criticizing letter to the editor by Rady en Verheijde in relation to our article represented in chapter 3.

Chapter 3-2 is a short letter to the editor, in reaction to an article by Fumis and Deheinzelin in Critical Care Medicine. The authors of the primary article promote active family involvement in the final decision of treatment withdrawal. In this letter we discuss why we oppose this kind of family involvement in end-of-life decision-making for several important reasons (practical and ethical).

In contrast to the single centre academic retrospective studies described above, **chapter 4** presents the result of a prospective observational study on withdrawal of life-sustaining measures in two complementary non-academic ICU's. In this study the effectiveness of the Dutch protocol for withdrawal of life-sustaining measures is evaluated, special attention is paid to the incidence of symptoms of discomfort and to the potential determinants (like dosages of opioids and sedatives and severity of illness) of time till death.

Chapter 5 is an editorial written as a comment on the "end-of-life-care" propositions of the Belgian Intensive Care Society. In this chapter we argue against the

proposed increase or introduction of medication in the absence of symptoms. In our opinion only the presence of symptoms justifies change in medication or increase of dosages.

SECTION II

Chapter 6 describes the ethical dilemma that occurred when a young woman requested for procurement of sperm from her almost brain dead partner, who was also a fully registered multi-organ and tissue donor. The ethical and legal pro's and con's are discussed within the perspective of the different European laws and regulations on this issue.

Chapter 7 discusses whether or not it is ethically defendable to ask patients who are fully conscious and that have made clear that they don't want any further treatment, to ask for organ donation before treatment is withdrawn.

Chapter 8 is an article focused on the definition of brain-death and on the discussion which tests should be at least performed, to establish a correct and reliable diagnosis of irreversible brain failure, in order to make an organ donation procedure eventually less frustrating and time consuming.

SECTION III

Chapter 9 comprises the general discussion, the limitations of the studies in the thesis and recommendations for future research.
Chapter 10 is the summary and conclusions section of the thesis in English.
Chapter 11 is the summary and conclusions section of the thesis in Dutch.

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SECTION I

2 Withdrawal of life-sustaining treatment in a mixed intensive care unit: most common in patients with catastrophic brain injury

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Abstract

Objective
To determine the incidence of withdrawal of life-sustaining treatment in various groups of patients in a mixed intensive care unit (ICU).

Design
Observational retrospective. Setting: University hospital mixed medical, neurological, neurosurgical and surgical ICU.

Patients
All patients admitted to the ICU between November 1, 2006, and October 31, 2007.

Results
1,353 Patients were admitted to our ICU between November 1, 2006, and October 31, 2007. During this period 218 (16.1%) patients died in the ICU, 10 of which were excluded for further analysis. In 174 (83.7%) of the remaining 208 patients life-sustaining treatment was withdrawn. Severe CNS injury was in 86 patients (49.4%) the reason for withdrawal of treatment, followed by MODS in 67 patients (38.5%). Notably, treatment was withdrawn in almost all patients (95%) who died of CNS failure. Patients who

died in the ICU were significantly older, more often admitted for medical than surgical reasons, and had higher SOFA and APACHE II scores compared to those who survived their ICU stay. Also SOFA scores before discharge/death were significantly different from admission scores. Of the 1,135 patients who survived their ICU stay, only 51 patients (4.5%) died within 28 days after ICU discharge.

Conclusions
In 83.7% of patients who die in the mixed ICU life-sustaining treatment is withdrawn. Severe cerebral damage was the leading reason to withdraw life-sustaining treatment.

Keywords
Intensive Care, End-of-life, Withdrawal of treatment, Subarachnoid Hemorrhage, Traumatic Brain Injury

INTRODUCTION

Over the last decades modern technology has allowed critically ill patients to survive longer. At the same time, it is increasingly accepted that continued aggressive ICU care is not always beneficial. Consequently, the dying process in the ICU frequently follows limitation of life-supporting therapies, with documented percentages up to 90% of all deaths preceded by some form of limitation.[1-5]

Physicians behaviour of withholding or withdrawing life-supporting measures is changing in time[5,6] and differs between regions and countries.[7] Withdrawing treatment is more common than withholding treatment in northern European countries and the US than in southern European countries like Italy and Portugal.[2] Besides the severity of illness[8], cultural-religious motives influence the approach and practise of end-of-life care.[2, 7]

The majority of studies to date have focused on either end-of-life issues[5, 9-11] or outcome for a single diseas.[12-16] Less data are published concerning the ICU patient population as a whole, irrespective of the underlying disease.[17] This would provide better insight in the total group of patients, in which treatment is withdrawn.

The objective of this study was to evaluate the incidence of withdrawal of life-sustaining treatment in various groups of patients in a single center university hospital mixed ICU in the Netherlands.

MATERIAL AND METHODS

STUDY DESIGN

We performed an observational retrospective study in the Erasmus MC University Hospital in Rotterdam, The Netherlands. The ICU is a mixed medical, neurological, neurosurgical and surgical ICU with a capacity of 28 beds. All patients admitted to the ICU between November 1, 2006, and October 31, 2007, were included. Institutional Review Board approval was waived, as it is not required in the Netherlands, when research concerns the use of anonymous data of deceased patients.

DATA COLLECTION

Data were collected using our patient data management system (PDMS), the electronic patient file and handwritten medical charts. We recorded demographics (age, gender), date of ICU admission, ICU admission diagnosis (Acute Physiology and Chronic Health Evaluation II diagnosis; APACHE II diagnosis), length of stay (LOS) in the ICU, severity of illness (APACHE II score), Sequential Organ Failure Assessment-score (SOFA-score) upon admission and before discharge/death, death in the ICU, and the 28 day hospital mortality. Diagnoses were categorized as multiple organ dysfunction syndrome/multiple organ failure (MODS/MOF), severe central nervous system (CNS) injury, acute cardiac arrest, pulmonary failure, kidney failure, liver failure, or acute hemorrhage. Withdrawal of treatment was recorded in a binary fashion.

STUDY DEFINITIONS

Some APACHE II diagnoses appear in both the operative and non-operative group, our PDMS does not distinguish between sepsis, post cardiac arrest, and post respiratory arrest. We assigned all patients in the aforementioned categories to the non-operative status. LOS was defined as number of consecutive days a patient was admitted to the ICU. We recorded 1 day if the admission was less than 24-hours, and the admission SOFA-score is identical to the SOFA-score at discharge/death. If the SOFA-score was incomplete, and no data were available for the concerning date, it was scored using previous values nearest in time. Only

patients who died in the ICU were recorded as death in the ICU. CNS failure was defined as irreversible catastrophic cerebral damage. If (multiple) organ failure was secondary to CNS failure, reason to withdraw therapy was noted as CNS failure. Patients were declared brain death if they met all criteria set under Dutch law. Withdrawal of treatment included withdrawal of mechanical ventilation and/or vaso-active drugs. If withholding treatment was the sole limitation, and no actual withdrawal took place, patients were classified as no withdrawal. Opioids and/or sedatives were administered in accordance with professional consensus and national guidelines. Occasionally, if delayed death was likely, patients were discharged to a ward and were categorized as ICU survivors.

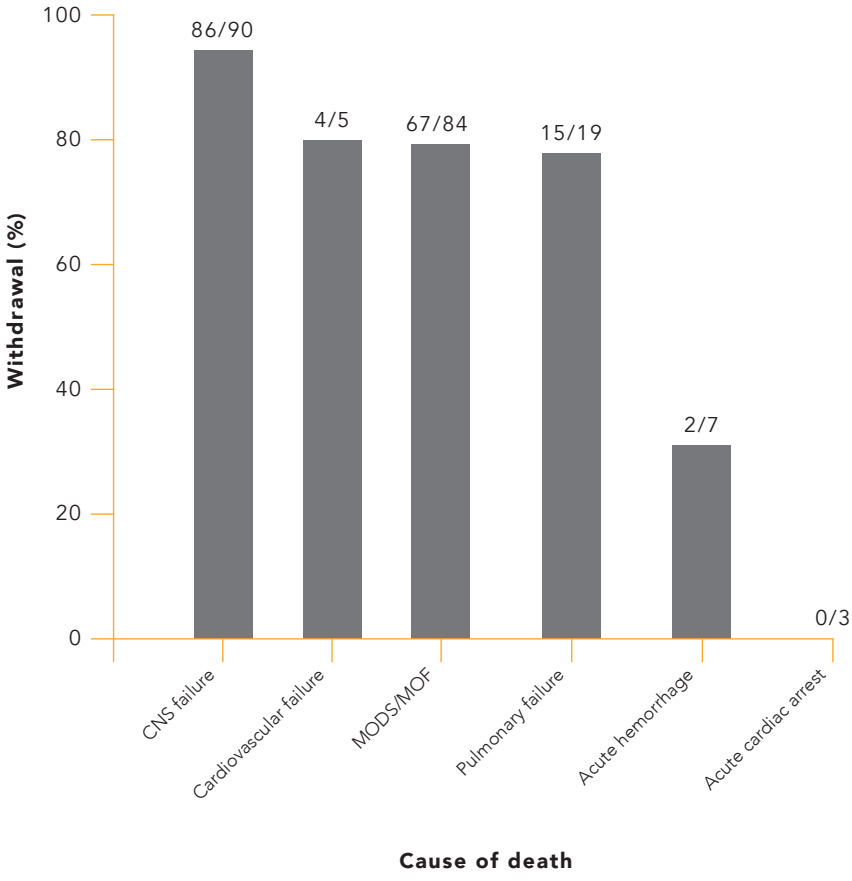
STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 15 for Windows (SPSS Inc, Chicago, IL, USA). Descriptive statistics were computed for all variables. Results are expressed in numbers and percentages, mean ± standard deviation for continuous parametric variables, and median and interquartile range (25-75% IQR) for continuous, non-parametric variables. Difference testing between groups was performed using the student t-test, Mann-Whitney U test, Wilcoxon signed rank test, or Chi-square test as appropriate. A p-value of $< .05$ was considered statistically significant. Missing values were excluded from analysis.

RESULTS

1,353 Patients were admitted to our ICU between November 1, 2006, and October 31, 2007. All patients were included in this study. During this period 218 (16.1%) patients died in the ICU. Population characteristics are shown in Table 1. Median age was 58 years, and 59.9% of patients were male. Patients who died in the ICU were significantly older, more often admitted for medical than surgical reasons, and had higher SOFA and APACHE II scores compared to those who survived their ICU stay. Also their SOFA scores before discharge/death were significantly different from admission scores. Of the 1,135 patients who survived their ICU stay, only 51 patients (4.5%) died within 28 days after ICU discharge. Of the 218 patients who died in the ICU, 9 patients were brain death and data of one patient were untraceable, leaving 208 patients available for analysis.

Figure 1. Withdrawal of treatment (n=174)



Values are presented as percentages; numbers above columns represent cases of withdrawal and total number of cases per cause of death. CNS failure; Central Nervous System failure. MODS/MOF; Multiple Organ Dysfunction Syndrome/Multiple Organ Failure.

Table 1. Study population characteristics

	All patients n=1,353	Survivors n=1,135	Non-survivors n=218
Age, years	58 (44-69)	57 (43-68)	62 (50-75)*
Male sex (%)	811 (59.9)	677 (59.6)	134 (61.5)
LOS, days	4 (2-8)	4 (2-7)	4 (2-11)
APACHE II diagnosis (%) [a]			
Surgical	539 (43.5)	485 (47.5)	54 (24.8)*
Cardiovascular	92 (7.4)	81 (7.9)	11 (5.1)
Gastro-Intestinal	199 (16.0)	185 (18.1)	14 (6.4)
Neurological	154 (12.4)	131 (12.8)	23 (10.6)
Respiratory	53 (4.3)	48 (4.7)	5 (2.3)
Renal	21 (1.7)	20 (2.0)	1 (0.5)
Other	20 (1.6)	20 (2.0)	0 (0)
Non-surgical	701 (56.5)	537 (52.5)	164 (75.2)
Cardiovascular	78 (6.3)	64 (6.3)	14 (6.4)
Gastro-Intestinal	73 (5.9)	60 (5.9)	13 (6.0)
Neurological	233 (18.8)	175 (17.1)	58 (26.6)
Respiratory	203 (16.4)	160 (15.7)	43 (19.7)
Renal	11 (0.9)	9 (0.9)	2 (0.9)
Sepsis	49 (4.0)	40 (3.9)	9 (4.1)
After cardiac arrest	26 (2.1)	11 (1.1)	15 (6.9)
Other	28 (2.3)	18 (1.8)	10 (4.6)
APACHE II score, mean ± sd [b]	20.5 ± 7.3	19.1 ± 6.7	27.7 ± 6.4*
SOFA score admission [c]	7 (4-10)	6 (4-9)	9 (7-13)*
SOFA score discharge [d]	5 (3-8)	3 (2-5)	10 (7-15)*°

*Values are represented as median (interquartile range), unless stated otherwise. LOS, length of stay; a 113 missing values (113 survivors); b 450 cases with ≥1 missing variable (377 survivors, 73 non-survivors); c 359 cases with ≥1 missing variable (321 survivors, 38 non-survivors); d 768 cases with ≥1 missing variable (729 survivors, 39 non-survivors); *p<0.01 compared to survivors; °p<0.05 compared to SOFA score on admission for both survivors and non-survivors.*

In 174 (83.7%) of these patients life-sustaining treatment was withdrawn (Figure 1). Severe CNS injury was in 86 patients (49.4%) the reason for withdrawal of treatment, followed by MODS in 67 patients (38.5%). In patients who died of primary CNS failure, treatment was withdrawn in 95%. The majority of patients with severe CNS injury was admitted with primary intracranial disorders (73%). Patients with intra cerebral-, subdural- or subarachnoid hemorrhage (ICH/SDH/SAH) and traumatic brain injury (TBI) accounted for 42.9% and 27.0% in the non-surgical and surgical group respectively (figure 2 and table 2). Craniotomy for ICH/SDH/SAH made up 69.6% of the surgical group.

Figure 2. CNS failure / APACHE II diagnosis (n=90)

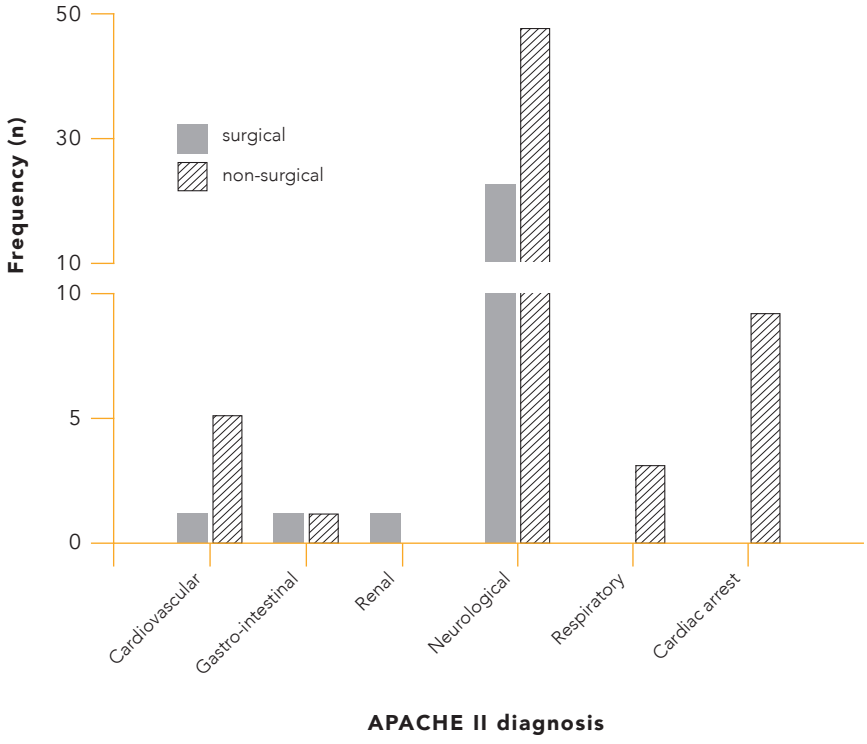


Table 2. CNS failure / APACHE II diagnosis (n=90)

	Surgical	**Non-surgical**
Cardiovascular	1	5
Gastro -Intestinal	1	1
Renal	1	0
Neurological	22 • 2x no WD craniot ICH/SDH/SAH • 3x cran neopl, 1x SHL, 18x ICH/SAB	47 • 1x no WD ICH • 17x SHL, 28x SAB/ICH, 2x epil
Respiratory	0	3
Cardiac Arrest	-	9 ▪ (1x no WD)
Total	25	65

DISCUSSION

This study determines the incidence of withdrawal of life-sustaining measures in various groups of patients in a mixed intensive care unit. In our population 16.1% of patients admitted to the ICU in the studied period died, this is in accordance with other European ICUs.[2,3] The primary cause of death was severe central nervous system (CNS) injury, whereas MODS was the second most common cause.

This finding is in agreement with Mayr et al.[17], who identified both CNS and cardiovascular failure as the most important risk factors for death in the ICU. However, in their study MODS was the leading cause of death. The difference in cause of death is likely due to differences in case mix. In contrast to our study, nearly half of their patients were admitted after cardiac surgery, whereas catastrophic CNS failure occurred only in a minority of patients.

In our study, withdrawal of treatment preceded death in 84% of cases, which is high compared to the percentages reported by Sprung et al. (47.4%)[2], and

Spronk et al. (53%).[1] Differences in cultural and religious background may explain this difference. Indeed, the ETHICUS study group has shown that limitations in life-sustaining therapy varies in practice between regions and different religions. Physicians in the northern countries were more likely to withdraw treatment than their southern colleagues.[2] In addition, Catholic, Protestant, and physicians with no religious affiliation tended to withdraw rather than withhold treatment as the form of limitation in life-supporting therapy compared to their Jewish, Greek orthodox and Moslem colleagues.[9] Finally, moral judgements on withholding versus withdrawing treatment may vary among physicians and medical staff. Although from an ethical point of view consensus exists that there is no moral difference between withdrawing or withholding treatment[18, 19] this is not general accepted[20] and physicians may be more reluctant towards withdrawing than withholding treatment.[21] In our hospital, the decision to withdraw therapy is made by the multidisciplinary team. A noticeable difference compared to the USA, where such decisions are made by the responsible physician in collaboration with family members or a surrogate decision maker of the patient.[19, 22] When treatment is believed to be futile by the multidisciplinary team, in most cases treatment is withdrawn rather than withheld.[23]

Among patients in whom treatment was withdrawn, a large percentage of patients with severe CNS failure were presented. Moreover, we found that treatment was withdrawn in almost all of the patients (95%) who died of CNS failure. Although the percentage found is high, this is in line with results reported by Sprung et al. where therapy limitations were most often made for acute cerebral diseases.[2] In addition, neurological failure was the second most quoted reason to limit treatment, and the reason in one of five cases in northern regions.[11] Again, differences in religion, culture and moral judgements may cause the difference in percentage in withdrawal of treatment in patients with severe neurological damage in our study and other authors. Hypothetically, another explanation exists and causes some concern. The decision to withdraw treatment depends on the expectation that patients with severe neurological damage have a "poor" prognosis and that on-going treatment is futile. To differentiate "poor" from "good" prognosis and to determine what is and what is not futile remains difficult. Also, withdrawing treatment inevitable leads to death in these cases and hence, the hazard exists of a

self-fulfilling prophecy in regard to withdrawing life-sustaining therapy in patients with severe neurological damage.[24] To avoid this particular trap caring physicians ought to determine the prognosis grounded on evidence-based studies lacking a large group of patients in which treatment is withheld or withdrawn.

We found a readmission rate of 11.4% that is comparable with rates reported in a large review[25], but higher than reported in recent studies (5.1-7.4%). [26, 27] This difference can be partially accounted for by differences in case mix. It is also possible that there are differences in ICU admission and discharge policies, because our hospital does not have high or medium care units.

Cook et al [28] studied withdrawal of mechanical ventilation in anticipation of death in the ICU. All patients were mechanically ventilated, 66.3% were successfully weaned from the ventilator, 17.2% died while receiving ventilation, and 19.5% had mechanical ventilation withdrawn, of whom 87.3% died in the ICU. More than 66% died after withdrawal of mechanical ventilation, vasoactive agents, and/or dialysis. Physician's perception that the patient preferred not to use life support, and the physician's prediction of a low likelihood of ICU survival were major determinants of withdrawal of mechanical ventilation. However, severity of illness and organ dysfunction were not associated with withdrawal of mechanical ventilation. In our study population, ICU non-survivors had a SOFA score of 12.5 (IQR 9-17) before death. Patients in whom treatment was withdrawn, had a median SOFA-score of 12 (9-17), compared to 14 (9-18) in patients with no withdrawal. When subdividing patients who died after withdrawal into CNS failure and no CNS failure, SOFA-scores are 10 (7-14) and 15 (11.25-17) respectively. This seems to be in accordance with Cook et al[28], but no conclusions can be drawn from these observations in the present study, because the missing values outnumbered the valid values.

LIMITATIONS

This was a single center, single country study, which may limit the generalizability of our results to other centers and countries. In addition, our population comprised a high proportion of patients with catastrophic cerebral injury; which in part can be explained by the fact that our hospital is one of ten trauma centers in the Netherlands (all patients with severe TBI in a region of 2,1 million inhabitants are

admitted to our hospital) and because we serve as a regional center for the (surgical/endovascular) treatment of patients with subarachnoid hemorrhage. Also, the withdrawal rate in this study may be underestimated. Although not standard practice, some patients were transferred to the ward after withdrawal of therapy when delayed death was likely. These patients were excluded from non-survivor analysis, and thus clouded both survivor and non-survivor data.

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3 The use of opioids and sedatives and time until death after withdrawing mechanical ventilation and vasoactive drugs in a Dutch intensive care unit

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Abstract

Objective

To study the frequency of withdrawal of mechanical ventilation and/or vasoactive agents, the time until death, dosages of opioids and sedatives in a Dutch academic ICU, and to compare these practices with international observations in this field.

Methods

Retrospective data were collected from the electronic and paper files of all patients who died after withdrawal of treatment in a Dutch ICU between October 2006 and February 2007.

Results

In this period, 471 patients were admitted to the ICU, of whom 88 died (18%). In 60 of these patients (68%), MV and/or VA was withdrawn. This group represented 13% of the total ICU population. Of the 60 patients for whom MV and/or VA was withdrawn, 54 (90%) died after withdrawal of MV (with or without VA). Six (10%) died after withdrawal of VA only, 33 (55%) after withdrawal of MV in combination with VA, and 21 (35%) after withdrawal of MV only. Death occurred after withdrawal of MV in combination with VA after a median of 30 minutes (IQR 10–195 min).

When only the ventilation was discontinued, the median time until death was 50 minutes (IQR 15–530 min). When only VA was withdrawn, patients died after a median of 45 minutes (IQR 20–715 minutes). Ten patients (17%) did not receive opioids or sedatives in their last hours. Fifty patients received opioids in their last hours. Fentanyl, with a median dosage at time of death of 100 µg/hr, was the most commonly used opioid. Forty (80%) of the 50 patients mentioned above received some kind of sedative until death. In the MV withdrawal group, 34 of the 54 (63%) received sedatives in the last hours of their lives: 16 (27%) received midazolam (median 10 mg/hr), 12 (22%) propofol (median 160 mg/hr) and 6 (11%) lorazepam (2.0 mg/hr). Sedatives were administered to all patients in whom only VA was withdrawn.

Conclusions

Dutch patients who die in the ICU, or die after discharge from the ICU, die after MV and/or VA are withdrawn. When treatments are withdrawn, death follows within one hour in most patients, which is a reflection of the severity of illnesses. At least 80% of patients receive opioids, and 67% receive sedatives until death.

Fentanyl is the most used opioid, whereas midazolam is the most used sedative. Dosages of opioids and sedatives did not significantly exceed the ranges described as usual in the international literature.

INTRODUCTION

With the introduction and technological development of ICUs as we know them now, patient survival has increased markedly, as has our ability to postpone death for an undefined period of time. Due to these developments, withholding and withdrawing active treatment has become an acceptable practice in many countries, including the Netherlands.[1-3] In this context, it is important to understand that withdrawal of treatment is not considered the same as euthanasia in the Netherlands. In many countries, this vision is shared; however, the debate on this issue is certainly not conclusive.[4,5] Although euthanasia is only justified in certain well-defined circumstances in the Netherlands, many doctors have stated or believe that Dutch doctors are more aggressive with life-ending treatments and withdrawals.

In the Intensive Care Unit (ICU), mechanical ventilation (MV) and administration of vasopressive agents (VA) are the most commonly used life-sustaining treatments. For reasons of disproportion, futility or at the request of the patient, the medical staff may decide to withdraw these treatments, which results in death of the patient within hours or days in almost all cases.[6]
The severity of illness and organ failure and the kind of treatment that is withdrawn are strongly correlated with the time until death.[7]
Withdrawal of life-sustaining treatment can result in distress, pain, restlessness, spasms, breathlessness and death rattle. Key quality measures for end-of-life care

include the timely assessment and effective treatment of these physical symptoms.[8-10] Pain and distress symptoms are normally prevented or suppressed with opioids, sedatives, and other selected medications. The supposed contribution of the dosage level of these medications to the time until death is still the subject of much discussion.[11] On the other hand, a growing body of evidence suggests that after the administration of opioids or sedatives, instead of shortening the dying process, dying is prolonged.[12-15]

Our primary objective was to study the frequency of MV and/or VA withdrawal in anticipation of death, the frequency of opioid and sedative usage, the dosages of opioids and sedatives, and the relation of these factors to time of death in our Dutch ICU. Secondly, we wished to compare our results with the existing literature from other countries, as there have not been any comparative studies published to date on this much-debated Dutch situation.

MATERIALS AND METHODS

SAMPLE

We collected data from all patients for whom life-sustaining treatment was withdrawn between October 2006 and February 2007 in the 27 bed ICU of the Erasmus MC University Hospital in Rotterdam, the Netherlands. Patients were from a mixed population of medical, general surgical, neurological, neurosurgical and trauma cases.

DATA COLLECTION

Data were collected from both electronic and paper patient files. We gathered information on MV and/or VA withdrawal, time until death, and data concerning the administration of fentanyl, morphine, midazolam, propofol and lorazepam to patients whose MV and VA were withdrawn. In the studied patient group, no other kinds of sedatives, opioids, barbiturates or muscle relaxants were used in this period. Additionally, we gathered data on background characteristics of the patient (i.e., gender, age, length of stay in the ICU, length of stay in the ward after discharge from the ICU, APACHE II score, SOFA score and primary admission

diagnosis). For data collection from already deceased patients who were not part of an interventional study, no informed consent or additional approval was necessary, as per Dutch law.[16] Treatment was withdrawn only after multidisciplinary consent, when patients failed to respond to therapy in the case of multiple organ failure, or when the inevitable poor prognosis of the acute disease became evident. Existing treatments were always withdrawn all together and not separately or consecutively. During the study period, there was no distinct, uniform protocol for end-of-life care in use by the ICU specialists.

ANALYSIS

The median duration of time until death following withdrawal of MV and VA was calculated. Retrospectively, three groups could be distinguished:

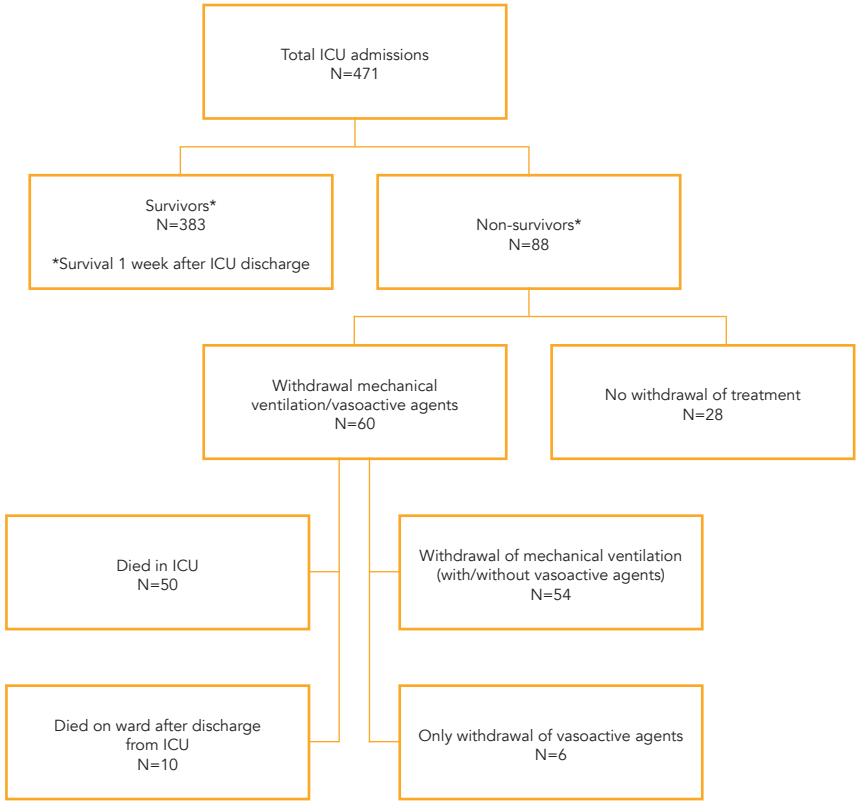
- Patients in whom MV in combination with VA was withdrawn.
- Patients in whom only MV was withdrawn, and no VA were present.
- Patients in whom only VA were withdrawn, and no MV was present.

The median quantities and ranges of opioids and sedatives administered per intravenous syringe pump infusion per hour and by bolus injection were registered. Analyses were conducted using SPSS 12.1 (SPSS Inc. Chicago, USA).

RESULTS

During the study period, 471 patients were admitted to the ICU, of whom 88 died. Sixty of these 88 patients died after withdrawal of treatment, as shown in Figure 1. Twenty-eight patients died spontaneously during the study period without withdrawal of VA and/or MV; these patients died as a result of withholding of therapy, unsuccessful CPR, cerebral herniation, fulminant therapy-resistant septic shock, or massive unstoppable bleeding after trauma. The general characteristics of the sixty patients who died after withdrawal of MV, VA or a combination of both are shown in Table 1.

Figure 1. Flow diagram of the study



MV AND/OR VA WITHDRAWAL

The general characteristics of the study population, the variable withdrawal rates and the incidences of use of opioids and sedatives is shown in Table 1.

MV and/or VA were withdrawn for 60 patients, representing 13% of all ICU admissions. Because a total of 88 patients died, 68% (n=60) of this subset of patients died as a result of withdrawal of MV and/or VA. MV was withdrawn in 11% (54) of all (471) ICU admissions, representing 61% of all patients who died. Of all patients admitted to the ICU, only 1.3% had only VA withdrawn, which represents 7% of all the patients who died in the ICU.

Table 1. The general characteristics of the study population

	N	(%)	Median (IQR)
Gender (male)	36	(60%)	
Age (years)			64 (52-73)
Length of stay in ICU (days)			4 (1-10)
APACHE II			30 (25-34)
SOFA score day 1 ICU			8 (7-11)
SOFA score day before withdrawal			8 (7-12)
Primary admission diagnosis ICU			
-Neurological	27	(45%)	
-Cardiovascular	10	(17%)	
-Respiratory	11	(18%)	
-Gastrointestinal/hepatic	9	(15%)	
-Renal	2	(3%)	
-Hematological	1	(2%)	
MV withdrawn	54	(90%)	
-only MV withdrawn	33/54	(61%)	
-MV and vasoactive agents withdrawn	21/54	(39%)	
Vasoactive agents withdrawn (no MV)	6	(10%)	
Received opioids until death	50	(83%)	
Received sedatives until death	40	(67%)	
Received opioids nor sedatives until death	10	(17%)	
Died in ICU	50	(83%)	
Died on ward	10	(17%)	

IQR=Inter Quartile Range. MV=mechanical ventilation

In 42 of the 60 patients, not only was ventilation terminated, but the endotracheal tube was also removed. One patient had a tracheostomy, which was not removed. Only four patients remained on the ventilator until death. Nine patients in whom MV was withdrawn were discharged to a special-care ward almost directly following cessation of MV therapy. After extubation, oxygen was not administered systematically. Twenty-one (35%) of the 60 patients died after withdrawal of MV in combination with VA, 33 (55%) died after withdrawal of MV alone, and 6 (10%) died after withdrawal of VA only. Fifty patients died in the ICU, and 10 died after discharge from the ICU to a non special-care ward. SOFA scores were higher in

patients for whom mechanical ventilation and vasoactive support were withdrawn than in patients for whom only mechanical ventilation was withdrawn (24 hours after admission: median 11 vs. 8, p=0.03; 24 hours before death: 11 vs. 7, p<0.01).

TIME UNTIL DEATH AFTER WITHDRAWAL OF LIFE-SUSTAINING TREATMENT

Death occurred a median of 30 minutes (IQR 10–195 min) after withdrawal of MV in combination with VA, as shown in Table 2. When only the ventilation was discontinued, the median time until death was 50 minutes (IQR 15–530 min). In our small series in which only VA was withdrawn, patients died after a median of 45 minutes (IQR 20–715 minutes). The differences in time until death between these three withdrawal categories were not statistically significant.

Patients who were transferred to the ward after the withdrawal of MV died after a median of 63 hours (IQR 13–192 hr). The one patient who was transferred to the ward after withdrawal of both VA and MV died 35 minutes after cessation of both therapies.

SEDATIVES AND OPIOIDS

Table 3 displays the cumulative quantities and dosage distribution of sedatives and opioids in all patients (n=60) who died after withdrawal of MV and/or VA for all three withdrawal categories and three different time periods.

Table 2. Time until death in three different groups after withdrawal of life-sustaining treatment

		Withdrawal mechanical ventilation - death				Withdrawal vasoactive support - death			
Mechanical ventilation and/or vasoactive support withdrawn	N	Median duration (minutes)	Interquartile range	Range	P*	Median duration (minutes)	Interquartile range	Range	P*
Total	60				0.30				0.45
Mechanical ventilation and vasoactive support	21	0:30	(0:10-3:15)	(0:05-35:50)		0:30	(0:12-1:40)	(0:08-35:50)	
Mechanical ventilation	33	0:50	(0:15-8:50)	(0:03-263:15)		-			
Vasoactive support	6	-				0:45	(0:20-11:55)	(0:11-17:45)	
Died in the ICU	50				0.89				0.64
Mechanical ventilation and vasoactive support	20	0:26	(0:10-1:45)	(0:05-28:00)		0:30	(0:11-1:12)	(0:08-28:00)	
Mechanical ventilation	25	0:30	(0:10-1:17)	(0:03-16:39)		-			
Vasoactive support	5	-				0:26	(0:18-9:25)	(0:11-17:45)	
Died in the ward	10				0.70				0.32
Mechanical ventilation and vasoactive support	1	35:50				35:50	-	-	
Mechanical ventilation	8	63:33	(13:14-192:26)	(5:15-263:15)		-			
Vasoactive support	1					9:58	-	-	

** Difference in time until death with Mann-Whitney U test for the three withdrawal categories in all patients, ICU patients, and ward patients.*

Table 3. Use of opioids and sedatives before and after withdrawal of mechanical ventilation and or vasopression. Administration by syringe pump.

	N#	Cumulative quantity till death / hours from withdrawal until death*			Dosage maximal 4 hours before death*			Dosage maximal 1 hour before death*		
Medication in total and per withdrawal groups		Med	(IQR)	(Range)	Med	(IQR)	(Range)	Med	(IQR)	(Range)
Fentanyl (mcg), total	35	88	(52-104)	(20-500)	100	(60-169)	(20-500)	100	(86-223)	(20-500)
• Withdrawal of mechanical ventilation and vasoactive support	15	100	(52-100)	(34-500)	100	(92-155)	(50-500)	100	(100-250)	(50-500)
• Withdrawal of mechanical ventilation	15	100	(50-148)	(20-250)	106	(50-192)	(20-250)	123	(50-213)	(20-375)
• Withdrawal of vasoactive support	5	73	(44-94)	(38-101)	100	(44-118)	(38-136)	100	(61-173)	(50-246)
P†		0.59			0.51			0.70		
Morphine (mg), total	15	6	(2.5-10)	(1.5-30)	5.5	(4-10)	(1-30)	6	(5-10)	(1-10)
• Withdrawal of mechanical ventilation and vasoactive support	3	10	-	(8-30)	20	-	(10-30)	10	-	-
• Withdrawal of mechanical ventilation	11	5	(2.5-10)	(1.5-10)	4.5	(3-10)	(1-10)	5	(3.5-10)	(1-10)
• Withdrawal of vasoactive support	1	6	-	-	6	-	-	6	-	-
P†		0.18			0.16			0.50		
Midazolam (mg), total	19	6	(5-12)	(2-25)	8	(5-14.5)	(2-25)	8.5	(5-15.5)	(2-25)
• Withdrawal of mechanical ventilation and vasoactive support	4	6	(4-9.5)	(3.5-10)	8.5	-	(5-10)	9	-	(5-10)
• Withdrawal of mechanical ventilation	12	6	(4.5-11.5)	(2-25)	6	(4-13)	(2-25)	8	(5-14.5)	(2-25)
• Withdrawal of vasoactive support	3	16.5	-	(5-20.5)	15	-	(5-20)	15	-	(5-20)
P†		0.49			0.55			0.77		
Propofol (mg), total	15	90	(63-144)	(4-240)	134	(41-236)	(4-415)	160	(41-270)	(4-758)
• Withdrawal of mechanical ventilation and vasoactive support	7	77	(40-144)	(4-205)	100	(8-160)	(4-231)	160	(8-160)	(4-300)
• Withdrawal of mechanical ventilation	5	108	(72-211)	(68-240)	323	(186-413)	(168-415)	495	(240-756)	(240-758)
• Withdrawal of vasoactive support	3	100	-	(42-108)	71	-	(42-100)	71	-	(42-100)
P†		0.47			0.03			0.04		
Lorazepam (mg), total	6	1	(0.6-4.9)	(0.3-14)	1.3	(0.7-5.5)	(0.3-14)	1.7	(0.7-5.9)	(0.3-14)
• Withdrawal of mechanical ventilation and vasoactive support	3	0.8	-	(0.7-14)	0.2	-	(0.8-14)	1.6	-	(0.8-14)
• Withdrawal of mechanical ventilation	3	1.3	-	(0.3-1.8)	1.4	-	(0.3-2.7)	1.8	-	(0.3-3.2)
• Withdrawal of vasoactive support	-	-			-			-		
P†		0.83			0.83			0.8		

*# N=50, 10 patients received no opioids or sedatives. † The differences in dosages between the three withdrawal groups were compared using the Kruskal-Wallis test. * Med= Median, IQR=Inter Quartile Range, Range=min-max dosages*

OPIOIDS

Fifty of the 60 patients (83%) who died after withdrawal of therapy received some kind of opioid. Thirty-five patients received fentanyl, and 15 patients received morphine. Fentanyl was discontinued in two patients four hours before death. As a result, 33 patients received fentanyl until death. The median overall dosage for fentanyl was 88 µg/hr, and the maximum dosage at any time was 500 µg/hr. Morphine was discontinued during withdrawal in four patients; therefore, 11 patients eventually received morphine until death. Six of the patients on morphine died on the ward. The median overall morphine dosage was 6 mg/hr, and the maximum dosage given at any time was 30 mg/hr. The dosage of opioids did not differ statistically among the three withdrawal groups at any time point. Furthermore, only eight patients received a bolus injection of opioids after therapy was withdrawn, as indicated in Table 4.

SEDATIVES

Forty of the 50 patients (80%) mentioned above received some kind of sedative until death. Nineteen patients received midazolam; it was stopped four hours before death in one patient. Overall, patients received a median dosage of 6 mg/hour. The highest median dosage (8.5 mg/hour) was observed in the MV withdrawal group in the last hour before death. The dosages of midazolam did not differ significantly between the three withdrawal groups.

Fifteen patients received propofol, and none of these patients were transferred to the ward. In patients on propofol, seven had both MV and VA withdrawn, five had only MV withdrawn, and in the remaining three patients only VA was withdrawn. Overall, the patients received a median dosage of 90 mg/hr; four hours before death, they received 134 mg/hr, and one hour before death, they received 160 mg/hour. Patients in whom only MV was withdrawn received significantly more propofol four hours before death and one hour before death than the other two groups (323 mg/hr versus 100 and 71 mg/hour, p=0.03; and 495 mg/hr versus 160 and 71 mg/hr, p=0.04, respectively). In the MV withdrawal group, 34 of 54 (63%) patients received sedatives in the last hours of their lives: 16 (27%) received midazolam (median 10 mg/hr), 12 (22%) propofol (median 160 mg/hr) and 6

(11%) lorazepam (2.0 mg/hr). Sedatives were also administered to all patients in whom only VA was withdrawn; three received midazolam, while three received propofol. Only six patients received lorazepam, and none of these patients were transferred to the ward. The median overall dosage of lorazepam was 1 mg/hr, and the maximum median dosage was 1.7 mg/hr one hour before death. Most patients were sedated by continuous intravenous syringe pump infusion. After withdrawal of treatment, only three patients received bolus injections of a sedative (midazolam was used 3 times, with a median of 5 mg/bolus). Twenty (33%) of the patients who died after withdrawal of therapy did not receive any sedative.

Table 4. Administration of opioids and sedatives, by bolus injection, in patients before and after withdrawal of mechanical ventilation.

	Doses before withdrawal			**Max dose 4 hours before death**			**Max dosage 1 hour before death**			**Dose after withdrawal of MV**		
	N	Median	IQR	N	Median	IQR	N	Median	IQR	N	Median	IQR
Fentanyl (mcg/hr)	4	100	(63-213)	4	100	(63-123)	2	175	(100-250)	1	50	-
Morphine (mg/hr)	8	7.5	(5-10)	4	8	(5-25)	3	10	(5-30)	7	10	(5-10)
Midazolam (mg/hr)	4	4	(1-9)	3	5	(1-10)	2	8	(5-10)	3	5	(1-10)
Propofol (mg/hr)	1	80	-	1	80	-	0	-	-	0	-	-
Lorazepam (mg/hr)	1	0.3	-	1	0.3	-	1	0.3	-	0	-	-

DISCUSSION

In our series, life-sustaining therapy was withdrawn in 13% of all ICU admissions. This is higher than reported in studies from other countries, in which withdrawal of therapy accounts for only 1 to 8% of all ICU admissions.[17-20] However, our study results are closer to findings from the ETHICUS study[7] (9.8%), the report of Vincent et al.[21] from Belgium (9%) and the results from the cohort survey in the UK[6], where a maximum withdrawal percentage of 9.9% was reported. Notably, the UK survey showed a remarkably high level of inter-hospital difference in the incidence of death as a result of withdrawal of treatment, which varied from 1.7 to 96%.[6] Therefore, our results will probably not be representative of Dutch ICUs in general.

The incidence of MV withdrawal with or without VA in our study was also higher than in other studies, which report that MV withdrawals occur in 4 to 39% of all ICU deaths.[17,19,20,22] In our study, only 7% of patients died after withdrawal of only VA, which is lower than reported in other studies, in which 9-59% of patients died after withdrawal of VA.[17-19,22,23] These differences may be explained by the fact that, in contrast to what is reported by Keenan and others, we did not use a fixed order for withdrawing the different elements of supportive therapy. As can be derived from Table 2, VA and MV are often withdrawn together. In addition to this, there is generally only a small group of incurably ill patients in the ICU who are VA-dependent, but not ventilation-dependent. These facts together explain our low incidence of VA withdrawal alone.

Some readers will explain our high percentage of withdrawal by the fact that withdrawal of unwanted or disproportionate life-sustaining therapy might be more accepted in the Netherlands than it is in the UK and some other Northern European countries.[7] Another, more likely, explanation for these data is the high percentage of acute catastrophic neurological diseases in our series. We hypothesize that ICUs that do not admit patients with severe neurological diseases will probably have lower rates of treatment withdrawal. Only one study has reported a comparably high number of acute neurological patients (51%), resulting in a death percentage due to withdrawal of treatment comparable to that in our study (11%), thus supporting our hypothesis.[17] Furthermore, our patients seemed to be more severely ill in comparison to samples from other publications. In our study,

the median Apache II score was 30, versus 24 or 25 reported by other studies.[24,19] It is reasonable to assume that patients with high Apache scores would be less likely to respond to therapy; as a logical result, treatment was withdrawn more often in our group. The decision to withdraw treatment in our ICU is always made by the medical staff and is based on multidisciplinary team discussions. It is not a joint decision by staff and the relatives of the patients, as is mentioned and suggested in other publications.[25,26] This approach is supported by Dutch law, which generally places medical professionalism above the rights and wishes of patients or proxies. No special selection is made for what therapy to withdraw or in which order. We prefer to withdraw all life-sustaining treatment at the same time to demonstrate to the family that the decision is final.

Although the relatives of the patient do not actively participate in the decision-making process itself, they are adequately informed in a timely and comprehensive manner, and special wishes are always taken into consideration. In addition, when desired or necessary, one of our religious advisers is always consulted. The exclusion of the family from the decision-making process is deliberate, to prevent the development of unnecessary guilt, stress, or even posttraumatic stress disorder (PTSD), as described by Azoulay et al.[27] The study by Azoulay shows that active participation in the decision-making process results in a higher level of guilt and stress, and that the stress level becomes even higher when the family believes that they are not adequately informed. Therefore, we focus on providing adequate information to the family and not on engaging them in the decision-making process.

The short survival time in our study is comparable to the results described by Keenan and Chan.[12,24] They show, as did our own findings, that most patients who are dependent on any kind of support die within one hour of withdrawal of therapy. This indicates that these patients, because of the severity of their diseases, as reflected by high Apache scores, were highly dependent on these therapies. Because family satisfaction with the process of withdrawing MV seems to be higher when the patient is extubated, the endotracheal tube is removed in almost all patients when MV is withdrawn in our ICU, even if this may be associated with shorter survival.[3] Our procedure is different from other studies showing that extubation is the least used procedure in the withdrawal of life-sustaining treatment.

It may be the fear of unwanted symptoms, such as acute stridor and death rattle, which keeps many intensive care specialists from implementing this procedure.[7,17,28] Most ICU specialists and fellows in our ICU are aware that opioids are not to be used as a sedative and that the administration of (increasing doses of) opioids does not necessarily hasten death.[12-15] Fentanyl is avoided for the treatment of breathlessness in cachectic patients or in patients with muscle weakness (e.g., patients with amyotrophic lateral sclerosis).[29] Specific doses of opioids and sedatives are less important than titration to achieve the desired effect. Therefore, no fixed limits are applied to dosages in our ICU. However, doses are preferably not increased without titration or in the absence of demonstrable signs of discomfort or distress. Although the majority of patients did receive opioids until the time of death, the dosages used were lower than those reported by other authors and are, therefore, not outside the boundaries of the clinical practice described by others.[12,14,24,30,31] On the other hand, the differences in the dosages could be explained by multiple other factors, many of which are not addressed in the different studies to which we are referring. For example, the level of pain the patient is expected to experience and the duration of morphine treatment before the decision is made for withdrawal may have influenced the amount of medication needed. The fact that morphine and fentanyl were discontinued in some cases in our study suggests that our opioid dosages were not increased in the absence of demonstrable signs of discomfort or distress, but were used for comfort care only and certainly not with the intention to hasten death. Although this seems to be a legitimate and logical conclusion, we are, nevertheless, aware of the thin line between initial intention and final result in the process of withdrawing treatment and the treatment of unwanted symptoms, as described by Sprung et al.[11] The observation that some patients in our study who died after withdrawal of therapy did not receive opioids is explained by the high percentage of patients with primary catastrophic cerebral damage, who were deeply comatose and showed no signs of suffering during the process of dying.

Sedatives are used for end-of-life care in our ICU to prevent and treat terminal restlessness and delirium, as well as to increase the overall comfort of the patient during dying. The most often used medications are midazolam and propofol. Lorazepam is a known independent risk factor for delirium;[32] thus, the use of this

agent is avoided as much as possible in end-of-life care, or only low doses are used. This is reflected in the low percentage of patients who received lorazepam in our study.

In the ICU setting, propofol is increased before death to quantities appropriate for palliative purposes, when necessary.[33,34] The sedative doses in this study were not increased outside the boundaries of intentional palliative practice and are lower than those reported by others.[12,14,24,30,31] The fact that one-third of the patients did not receive any sedative can again be explained by the high percentage of deeply comatose patients with primary catastrophic cerebral damage. Indeed, 16 of the 27 patients who were admitted for acute neurological diseases did not receive continuous sedation.

STUDY LIMITATIONS

This study has certain limitations that should be taken into account when interpreting the data. In other international studies, in contrast to this study, no clear distinction is made in the different life-sustaining treatments that are withdrawn. In these series, all life-sustaining treatment was withdrawn in 2.8%, 9.9% and 10.4% of all ICU admissions, without making any sub-classification as to the type of life-sustaining treatment used and withdrawn.[6,7,35] For this study, we used different sources of information. In the ICU, we used electronic patient files. Regrettably, time registration is not always accurate in these files, as the registration of vital signs is sometimes turned off to prevent unwanted alarms, for the sake of piety, when a patient is dying. Therefore, the exact time of death cannot always be found in the electronic medical record. For this reason, some of the recorded times might not have been fully accurate; thus, corrections were made with the help of the paper files. In our study, we only looked at patients in one closed-format academic ICU. As a result, our findings may not be applicable to other Dutch (academic) ICUs or ICUs in other countries.

In addition, according to the reports in the patient files, most families seemed satisfied with the quality of communication and the implementation of the procedures, and there was a low incidence of conflicts regarding withdrawal of treatment issues. However, there was unfortunately no standardized and validated method, such as the FS-ICU, available in the Netherlands to measure family and/or

nurse/doctor satisfaction in the ICU during the study period.[36] In this study we did not focus on the possible relationship between individual dosages of opioids and sedatives and the time until death.

Finally, seasonal influences (e.g., the high percentage of severe brain injury due to traffic incidents in the winter) cannot be ruled out, as we only gathered information for the period between October and February.

CONCLUSIONS

MV and/or VA are withdrawn in the majority of patients who die in the ICU or who die shortly after discharge from the ICU. When these treatments are withdrawn, most patients die within one hour, reflecting the severity of the underlying illness, as expressed by the high SOFA and APACHE scores. Eighty percent of patients who died in the ICU after withdrawal of life-sustaining treatment received opioids, and 67% received sedatives until they died. Fentanyl was the most commonly used opioid, and midazolam was the most commonly used sedative. Opioids and sedatives were used in normal doses up to the optimal titration for relief of symptoms. This study suggests that in our ICU, after withdrawal of MV and vasopressive agents, opioids and sedatives are used in generally accepted dosages, which are comparable to the dosages reported in other studies. This is in contrast with what is often suggested about Dutch ICU end-of-life practices. Further qualitative and quantitative research is needed to better describe end-of-life care in Dutch ICUs, thereby facilitating improvements in quality of care in the near future.

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3-1 The confounding effects of pharmacokinetics and pharmacodynamics of sedatives and opioids on time to death after terminal withdrawal of life-support in the intensive care unit.

IN RESPONSE TO M. RADY EN J. VERHEIJDE

Epker, Jelle L.

Kompanje, Erwin J.O.

Published in:

Anesthesia & Analgesia, 2011

DEAR EDITOR,

Rady and Verheijde suggest, that we made an incorrect or unreliable analysis with our data concerning the relation of opioids and sedatives and the time till death.[1] This is surprising, because we deliberately refrained from a statistical analysis in our publication, as clearly mentioned in the limitations section. Because several other studies did show that in terminally ill patients the contribution of sedatives and opioids to the time till death is negative or can't be proven, we used these results for our discussion.[2-4] The study referred to, was not published when our article was accepted and deals with an absolute different population than discussed in our article.[5] Both SOFA and APACHE scores are high in comparison with other studies. This logically implies that MOF has a high incidence in our population. Together with the fact that treatment is withdrawn at once and not consecutively, it is inevitable that patients die within a very short time.

We did not show data about the level of discomfort, however, the dosage ranges of sedatives and opioids 4 hours before death, are not very different from the maximum dosages in the last hour, making it plausible that the standard sedation and pain medication was continued and not automatically increased after the withdrawal. The article referred to, discusses medication use in the neonatology departments, again a totally different patient population. Pharmacodynamics are indeed different in critically ill patients with MOF compared with "normal" patients. The question however is: "should we take these alterations into account, when we already do titrate medication only till the desired effect is reached?" Besides, to our knowledge there are no studies measuring the pharmacodynamics of sedatives and opioids in terminally ill ICU patients with the aim to get a better dose effect relation, so we wouldn't know how to implement the advice given.

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3-2 Respiratory support withdrawal in intensive care units: international differences stressed and straightened!

J.L.Epker

Y.J. de Groot

E.J.O. Kompanje

Published in:

Critical Care, 2011

DEAR EDITOR,

With great interest we read the article of Fumis and Deheinzelin about withdrawal of respiratory support in Intensive care Units.[1] We are convinced that the subject is of interest for the ICU community, but think that some of the conclusions are somewhat disputable.

First, we agree with the authors that family involvement in the withdrawal process is important, however this does not necessarily imply they should be joining the withdrawal decision-making. This was already demonstrated by Azoulay et al, who showed that direct participation in the withdrawal decision of family members is directly associated with feelings of guilt and development of posttraumatic stress responses.[2]

Second, the authors state that European ICU physicians are, in contrast with their North American colleagues, less inclined to withdraw treatment. This statement is not in concordance with our own experience. The withdrawal rate in our Dutch ICU is 83% of the patients who died in the ICU.[3] This result is fully supported by the ETHICUS study, which described that withdrawal of treatment is a generally accepted form of end-of-life care in Europe and especially Northern Europe.[4]

Finally, in our opinion it is the treating physician, who, after consultation of his colleagues, has the knowledge and experience to make a clear and fair judgment concerning the prognosis of a patient. In case of a poor prognosis it is the duty of this physician to make the withdrawal decision clear to and acceptable for the patient, the relatives and the nurses.

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4 An observational study on a protocol for withdrawal of life-sustaining measures on 2 non-academic Intensive Care Units in the Netherlands.

FEW SIGNS OF DISTRESS, NO SUFFERING?

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Abstract

Context

Because anticipation of death is common within the ICU, much attention must be paid to the prevention of distressing signs and symptoms, enabling the patient to die peacefully. In the relevant studies on this subject, there has been a lack of focus on measuring determinants of comfort in this population.

Objective

To evaluate whether dying without distressing signs after the withdrawal of life-sustaining measures is possible using a newly introduced protocol and to analyze the potential influence of opioids and sedatives on time till death.

Methods

A prospective observational study, in two non-academic Dutch ICUs after the introduction of a national protocol for end-of-life care. The study lasted two years and included adult patients in whom mechanical ventilation and/or vaso-active medication was withdrawn. Exclusion: All other causes of death.

Results

In the study period 450 patients died, 305 patients were eligible, 241 were

included. Ninety percent of patients was well sedated before and after withdrawal. Severe terminal restlessness, death rattle or stridor was seen in less than 6%. Dosages of opioids and sedatives increased significantly after withdrawal, but did not contribute to a shorter time till death according the regression analysis.

Conclusions
The end-of-life protocol seems effective in realizing adequate patient comfort. Most patients in whom life-sustaining measures are withdrawn are well sedated and show few signs of distress. Dosages of opioids and sedatives increase significantly during treatment withdrawal; however, do not contribute to time until death. Dying with a minimum of distressing signs is thus practically possible and ethically feasible.

Keywords
Signs of discomfort, intensive care, withdrawing of life-sustaining measures, time till death, opioids and sedatives, peak pressure.

INTRODUCTION

The most used life-sustaining measures on the ICU are mechanical ventilation and vaso-active medications. As it is lifesaving for many patients, over the last decade, a worrying trend has been noticed. Advanced life-sustaining measures are used in patients with poor long-term expectations secondary to more chronic organ dysfunction, co-morbidity and poor quality of life.[1] This can lead to the conclusion that the use of ICU measures is in certain cases disproportional. Withholding and/or withdrawing these life-sustaining measures (WOLSM) have become common decisions that precede death in ICUs worldwide. There are however striking differences regarding the frequency and practice of WOLSM among ICUs in Europe, North America and for example China.[2-5]

Rates of WOLSM sometimes vary within the same country and may depend on the initial diagnosis [6,7] and eventually range from 1.7% up to 85%.[5-8] The place where patients in terminal stages of their illness die varies. For example, 20% of deaths in North America follow ICU-admission, whereas, in the Netherlands, only 11% of deaths occur after admission to the ICU.[9-12]

As anticipated dying is common on the ICU, much attention should be dedicated to the prevention and treatment of distressing symptoms and signs, as pain, anxiety, agitation, restlessness and dyspnea to enable the patient to die peacefully.[13-16]

Unfortunately, in some relevant studies for this subject, the level of (dis)comfort of the patients or the evaluation or prevention of distressing signs and symptoms

are not clearly evaluated.[8, 17-22] Several individual countries have published studies on their country specific ICU populations and whether or not and how and when WOLSM is done.[8, 18, 19, 21-25] The only available article from the Netherlands describes a single center academic retrospective study.[17] In 2006 a concept guideline specifically designed for WOLSM, including advices on the prevention of distressing signs and symptoms on the ICU, was published.[26, 27] This guideline was adopted as the national end-of-life protocol by Dutch Intensive Care Society in 2008. Walling and colleagues showed in that same year that a protocol for end-of-life care symptom management is indeed feasible and useful.[28]

We studied end-of-life practice on two Dutch ICUs in two years after the introduction of the national protocol, with a focus on distressing signs and symptoms and the use of opioids and sedatives after WOLSM. Opioids and sedatives are the medications of choice in treating pain and various forms of distress in end-of-life care, however the assumption that the use of these medications might hasten death has made many doctors reluctant to use or increase dosages of these drugs. We wanted to analyze if the contribution of opioids and sedatives to the time till death is relevant in the case of severely ill ICU patients.
As far as we know this is the first study that actually describes and quantifies the level of signs of discomfort in an ICU population after WOLSM.

METHODS

STUDY DESIGN

We conducted a two-year prospective study that spanned from late 2008 until the middle of 2011. The study included all patients from two non-academic Dutch ICUs in whom mechanical ventilation (MV) and/or vaso-active medication (VAM) was to be withdrawn.

STUDY ICU'S

Two ICUs participated in this study. ICU-1 (14 beds) is one of the three largest level III non-academic ICUs with both cardiopulmonary and traumatology facilities

in the Netherlands. ICU-2 is a level I ICU that has 6 ICU beds and is part of a Protestant-Christian teaching hospital. Both hospitals are situated in the populated Western region of the Netherlands. These ICUs were selected because of their location, specific characteristics (as described above) and the presence of a team of dedicated ICU research nurses. The study itself was designed to be fully nurse-driven in order to prevent doctors' bias in the timing of WOLSM and the administration or registration of drugs.

INCLUSION AND EXCLUSION CRITERIA

This study included only adult (18+) patients in whom MV and/or VAM was scheduled to be withdrawn. Excluded from the study were brain-dead patients, patients who died spontaneously and patients who died after euthanasia. Euthanasia i.e. death on clear request of the patient by medication that is intended to terminate the life of the patient instantaneously (Dutch law definition of euthanasia), is, although allowed by legal provision extremely rare in the ICU setting, even in the Netherlands, and is therefore not further discussed in this study.[29]

DATA COLLECTION

At the time when the definitive decision was made to change the focus of treatment of the patients from curative to palliative end-of-life care, which included the withdrawal of MV and/or VAM, the research nurses initiated the process of inclusion and data registration, without informing the doctor involved. Information about the quality of decision-making and the motivation for the withdrawal decisions, were extracted from the patient files, if documented, or else noted as observed by the nurses.

T0 was defined as the moment just before the actual withdrawal of life support. After T0, the patient's sedation level, signs of discomfort, and medication dosages were scored every 15 minutes. General patient data, as well as data on disease diagnosis, disease severity scores and medication use, were also collected. For the analyses, the different opioids were all recalculated to morphine equivalents, as 10 µg fentanyl and 1 µg sufentanil are both equivalent to 1 mg morphine. Dosages of propofol and the VAMs are all expressed per kilogram of body

weight. In total, 14 different disease categories were defined. Both Rass and Ramsey scales were used to measure sedation levels. Signs of discomfort, including death rattle, stridor and terminal restlessness, were scored using a 5-point scoring system (Table 1).

Table 1. Discomfort scoring scales

Movement	**1** No movements **2** Occasional light movements of limbs **3** Frequent movements of limbs (>10 times/min) **4** Frequent and strong movements of limbs (level of risk of dislocation of iv lines) **5** Frequent and strong movements of head and limbs (the patients "crawls" in bed)
Stridor[1]	**1** No stridor **2** Soft stridor (audible next to the head-end of the bed) **3** Clear stridor (audible from before the bed-end) **4** Heavy stridor (already audible outside the room) **5** Extreme stridor i.e accompanied with inter-costal indrawings
Death Rattle[2]	**1** No rattle audible **2** Soft rattle (only audible just next to the head of the patient) **3** Mild rattle (audible at the bedside of the patient) **4** Clear rattle (audible from before the bed end) **5** Loud rattle (already audible outside the box)

[1] The abnormal, high-pitched sound produced by turbulent airflow through a partially obstructed airway at the level of the supraglottis, glottis, subglottis, and/or trachea
[2] The gurgling sound that originates from expirated air passing through a fluid collection (i.e not swallowed saliva) in the oro- or retropharynx

Data for sequential organ failure assessment (SOFA) score calculations were collected retrospectively when necessary. The potential predictors of the time until death after WOLSM were identified by a multidisciplinary intensive care research group already before the study began and consisted of the following: age, gender, body weight, SOFA score on day 1, SOFA score on the day of

withdrawal, APACHE II score, dosages of (nor)epinephrine, positive end-expiratory pressure (PEEP) level, peak pressure, inspired oxygen fraction (FiO2), length of stay (LOS) and (change in) dosages of opioids and sedatives.

ETHICAL APPROVAL

In the Netherlands, by law, pure observational studies with no intervention(s) are without exception exempt from IRB approval. The study described in this report was strictly observational and patients were treated with the standard of care. Therefore a request for approval for this study by the ethics committee was waived. Moreover under Dutch law, data of deceased patients may be used for publications and scientific research without specific consent if the data are fully redacted.[30] Since all the patients in our study died, all data were freely available from the hospital records without the specific permission of the patients or proxies.

STATISTICAL ANALYSIS

Patient data that were generated from consecutive observations, such as SOFA scores, were compared using paired t-tests. Potential predictors of time until death after WOLSM were evaluated using standard linear regression models instead of cox regression as all patients died. So the only between-patient variation in outcome is the time to the event (death) and not the event itself. Statistical analyses were performed, and graphs were created using IBM SPSS Statistics version 22.0 for Mac 2010 and Prism 5 for Mac OS X (GraphPad Software Inc., 2010).

RESULTS

GENERAL CHARACTERISTICS OF THE STUDY POPULATION

During the study period, 430 patients died. All ICU deaths in the study period were extracted from the general hospital administration and compared with the ICU study population deaths. Because during the study period 24/7 coverage for eligibility screening by the research nurses could not be offered, 125 patients were not screened. No patients were missed during the presence of the research nurses. In the eligible group, 79% of the patients died in the ICU after the withdrawal of MV and/or VAM. Eventually, 241 patients were included, as shown in Figure 1.

Figure 1. Flow diagram of the study

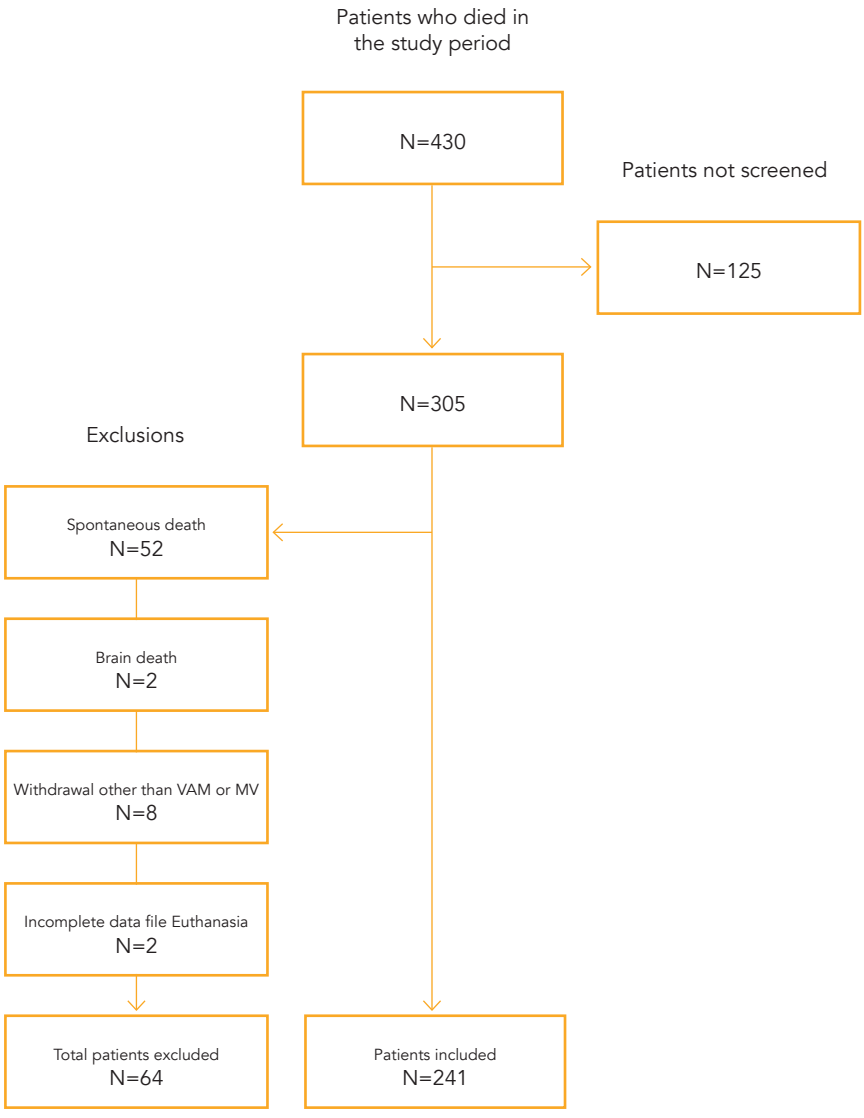

Table 2. The general characteristics of the study population and the reasons for admission

	Result/Number	Percentage
Age (mean in years ± SD)	70.51 ± 0.855 N = 241	
Male **Female**	142 99	58.9% 41.1%
Length of Stay (mean in days ± SD)	6.95 ± 0.548	
APACHE II score (mean)	30.5 ± 9.6 N = 215	89
SOFA score day 1 (mean ± SD)	10.24 ± 3.5 N = 241	100
SOFA score day 2 (mean ± SD)	10.47 ± 3.49 N = 169	70
SOFA score at day of withdrawal (mean ± SD)	12.26 ± 3.5[1] N = 241	100
Weight (mean in kg ± SD)	77.33 ± 1.045 N = 237	98
Peak pressure of ventilation (mean in mmHg ± SD)	27.15 ± 0.633 N = 212	88
Reason for admission	N = 241	100
Sepsis	71	29
Out-of-hospital cardiac arrest	50	21
Primary cardiac disease	27	11
Respiratory	21	9
Post-cardiac surgery	20	8
Neurological or Neurosurgical	15	6
Bleed (non-GI)	7	3
Hematological disease	7	3
Other	23	10

[1] *$p < 0.0001$ compared with the SOFA score on day 1*

The general characteristics of these 241 patients are described in Table 2.
There were no statistical differences between the general patient characteristics of the first and the second study year. The mean age of the non-eligible patients was 68.1 years and was not significantly different from that of the patients who were included in the study ($p = 0.16$). The mean Apache II score in the unscreened patient group was 27.3 ($p = 0.02$).

DIAGNOSTIC CATEGORIES

The distribution of the different admission categories is shown in Table 2.

DECISION-MAKING, RESPONSIBILITY AND MOTIVATION

The most common reasons that were mentioned as motivation for WOLSM were futility and/or the disproportionate use of ICU resources. In 56% of the cases, the decision was made after a multidisciplinary consultation. In 20% of the cases, the decision was made by the medical ICU team but without a multidisciplinary consultation. In 13% of the cases, a single doctor was responsible for the decision; however, 90% of these individual decisions were made during weekends, evenings or nightshifts. Fully shared decision-making was mentioned in 9% of cases. WOLSM happened two times on the request of the patient, and in two cases, family demand was the primary motivation.

VASOACTIVE MEDICATION, OPIOIDS, SEDATIVES AND MUSCLE RELAXANTS

The dosage characteristics of the intravenous medications that were used during the study period are described in Table 3. The overall dosages of propofol, midazolam and morphine equivalents increased significantly from T0 to T-final. In hospital 2 the rise in opioid dosages after withdrawal was not statistically significant. Muscle relaxants were used in only one patient with therapy-resistant myoclonus; ventilation, however, was continued until circulatory arrest.

WITHDRAWAL RATES AND DISCOMFORT AND SEDATION SCALES

The incidences of WOLSM-related signs of discomfort and the sedation scales are described in Table 4.

During the second year of the study period there were significant more extubations. Overall the incidence in the first year was 47% compared to 74% in the last year ($p < 0.001$), however incidences and severity of stridor and death rattle remained the same. Eight patients received butylscopolamine and/or diuretics for the prevention of death rattle. One patient received steroids in anticipation of stridor. None of these patients eventually scored grade 4 or 5 (severe) on the discomfort scale. At T0, 15 patients had a Rass score between -1 and 2 and a Ramsey score between 1 and 4. A change in sedation scores after withdrawal was observed in 47 patients, but these changes were observed mainly in lightly sedated patients due to the initiation of or increase in sedatives and/or opioids in this group.

TIME UNTIL DEATH

The median time from withdrawal until death is 20 min (Table 4). None of the 241 patients survived after WOLSM. Within 90 minutes of WOLSM, 80% of the patients had expired. Regression analysis of the potential predictors of the time until death in our model (R2 0.236 and F 3,769, $p <0.0001$) showed that ventilation peak pressure is the only significant predictor of a shorter time until death (beta = -0.205, $p = 0.032$). The only significant predictor of a longer time till death is the change in opioid equivalents (beta 0.326, $p=0.003$).The complete overview of the regression analysis coefficients is shown in Table 5.

Table 3. Intravenous perfusorpump medications used in the study

	Number	Percentage	Mean ± SD	Median	IQR ranges
Dobutamin maximum dosage[2]	94	39	4.6 ± 3.188	4.0	2.0 – 6.0
Norepinephrine maximum dosage[2]	170	71	0.62 ± 0.6	0.4	0.15 - 0.96
Adrenaline maximum dosage[2]	20	8	1.11 ± 1.2	0.7	0.2 - 1.8
Opioids start dosage T0	185	77	11,7 ± 8,38	10	5 - 15
maximum dosage[3]	213	88	14.04 ± 8.34*	12	6-18
Midazolam start dosage T0	111	46	12.2 ± 7.5	10	5 - 17
maximum dosage[4]	129	54	13.8 ± 9.8*	10	8-20
Propofol start dosage T0	78	32	186.8 ± 96.91	200	100 - 250
maximum dosage[4]	83	34	213.7 ± 113.2*	200	150 - 300
Propofol maximum dosage[5]	83	34	2.98 ± 1.57	2,6	1.76-3.6

[2] µg/kg/min
[3] morphine equivalents in mg/hr
[4] mg/hr
[5] mg/kg/hr

* Significant change p< 0.002

Table 4. Withdrawal rates, sedation levels, discomfort scales and time till death

Withdrawal rates	**Number**	**Percentage**
Mechanical ventilation present (MV)	231	95
Withdrawal of MV	216	93
Detubation after withdrawal of MV	141	65
Tracheostomy	9	4
Vasoactive medication present (VAM)	196	81
No VAM	45	19
VAM withdrawn	180	92
MV and VAM withdrawn together	157	65
VAM not withdrawn	16	8
Sedation levels		
Rass T0 -5/-4	188/19	78/8
Ramsey T0 6/5	185/34	77/14
Discomfort symptom scales		
Terminal restlessness		
- Severe (grade 4/5)	11	5
- Moderate (grade 3)	7	3
Death rattle		
- Severe (grade 4/5)	10	4
- Moderate (grade 3)	31	13
Stridor		
- Severe (grade 4/5)	8	3
- Moderate (grade 3)	17	7
Time until death	N=241	100
mean in minutes ± SD	111.64 ± 17.16	
median in minutes	20	

Table 5. Overview of the regression analysis coefficients

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	344,377	246,627		1,396	,164
	Age	,635	1,509	,030	,421	,674
	Sex	49,742	42,350	,086	1,175	,242
	Body weight	-1,069	1,348	-,058	-,793	,429
	LOS ICU	4,624	2,596	,128	1,781	,077
	SOFA score admission day	-2,764	7,434	-,032	-,372	,710
	SOFA score withdrawal day	-3,998	7,289	-,049	-,549	,584
	APACHE II score	-,364	2,324	-,012	-,157	,876
	PEEP level	-2,509	6,656	-,036	-,377	,707
	Peak pressure	-6,671	3,097	-,205	-2,154	**,033**
	FiO2	,185	,732	,019	,252	,801
	Withdrawal of MV	7,865	69,482	,008	,113	,910
	Norepinephrine	-30,635	41,780	-,061	-,733	,464
	Max. morfine equivalents	-2,027	2,399	-,092	-,845	,399
	Change in opioids	8,310	2,728	,327	3,046	**,003**
	Propofol mgram/kg/hr	3,866	13,216	,023	,293	,770

[a] Dependent Variable: Minutes till death after withdrawal of life-sustaining measures

DISCUSSION

Characterization of factors that predict time to death after WOLSM may help physicians to inform relatives of the dying patient and alleviate some of the anxiety resulting from uncertainty regarding the time course to death.[31]

Until now six studies have been addressing the subject of time till death after WOLSM for severely ill ICU patients.[12, 32-36] However, although each study in itself is interesting and illustrative for local habits and practice of WOLSM, they all have unfortunately one or more major shortcomings; like small sample size[33], not including sedatives or opioids in the analysis[34-36], the use of retrospective data[12] or being a single center study.[32, 34, 36] Several other studies have described the practice of WOLSM and the dosages of opioids and sedatives used but failed to report whether the patients were comfortable or well sedated or not. The absence of such essential information makes it impossible to compare results regarding how well end-of-life care was provided.

SEDATION LEVELS AND SIGNS OF DISCOMFORT

Pain, anxiety and dyspnea are probably the most important signs and symptoms to prevent when life sustaining measures are withdrawn, it is however very difficult to asses these "symptoms" in a population that is already deeply sedated and treated with opioids even before WOLSM. This is logical because most patients are severely ill and mechanically ventilated and would therefore be in pain and distress if no medication is given.[37] Therefore we focused on terminal restlessness as a representative sign for pain, dyspnea as well as anxiety. Death rattle and stridor might be distressing for the patient, however most of the times it is a stress factor for the attending family and should therefore be anticipated.[16]

Most patients were already well sedated even before WOLSM, only a few patients showed more signs of awareness after WOLSM than before. The majority of patients who had a change in sedation level changed from a shallow level of sedation to a deeper level, this in concordance with the marked increase of opioids and sedatives dosages in the same period.

The most frequently scored combination of moderate and severe signs of discomfort was death rattle, with an incidence of 17%. This is however not surprising because terminal extubation is an essential part of this new WOLSM protocol. Moreover, death rattle is also outside the ICU a very frequently observed sign in dying patients. The incidence of severe death rattle was only 4%. The incidences of terminal restlessness and stridor appear to be low, but this is hard to interpret because there are, as far as we know, no publications on this issue available.
As already mentioned in the result section, the incidence of terminal extubation increased over the 2 years. Nevertheless the incidences of death rattle and stridor did not increase. Apparently the reluctance to remove the tube after withdrawal of life-sustaining measures declined gradually, most likely because of the low incidences of distress factors encountered and the effectiveness of the preventive measures advised in the protocol.

OPIOID AND SEDATIVE USE

The majority in our population is receiving sedatives and opioids as a standard of care, resulting in adequate sedation at T0. Similar to what is described in other studies we saw a significant rise in the dosages of opioids and sedatives in the last hours of life.[17, 32, 34] We think that when death is imminent, these medications should be increased in a goal directed way, not focusing on the dosage level but on the individual patient so that suffering is alleviated and optimal patient comfort is achieved. The median dosage of morphine (12 mg/hr) is lower than described in previous reports.[25, 32] The fact that the opioid dosages did not increase significantly in the Protestant hospital is in concordance with the fact that Dutch religious people are reluctant in the use of opioids if an earlier death may be the result.[38] The statistically significant attribution of the increase in opioids to the lengthening of time till death supports however the hypothesis that goal directed use of opioids is "ethically" safe.[34, 39]

Chan et al. report the use of sedatives in only 40% of the total population and Rocker et al. in 45%, with only 3.4% using propofol.[25, 32] The comparison of sedatives is more complicated, because in contrast with the above-mentioned studies, in our study propofol is used as an alternative for benzodiazepines in

40% of patients receiving a sedative (86%). Notably the mean maximum dosage after withdrawal adjusted for bodyweight does in our study not exceed the 3 mg/kg/hr. The dosages of midazolam seem to be slightly higher than reported by Rocker et al. and Chan et al. However in their studies lorazepam in higher dosages is described, which is rarely seen in Dutch ICUs, because lorazepam is recognized as an independent risk factor for delirium and therefore abandoned.[40, 41]

AGE AND DISEASE SEVERITY

The patients in the study are 6 years older than the average Dutch ICU patient.[10] The mean Apache II and SOFA score in our cohort were 31 and 12 respectively. The combination of advanced age and (multi)organ failure is a strong predictor of death.[42, 43] The frequently observed combination of the two explains why inappropriateness of therapy is often mentioned as the key point in the decision process of withdrawing life-sustaining measures in this study.

PROCESS OF WOLSM, TIME TILL DEATH AND SEVERITY OF SUFFERING

Predicting time till death is not easy in a general ICU population as demonstrated by Munshi et al.[44] However some representative studies showed in concurrence with our data that high ventilator settings like PEEP, FiO2 or peak pressure are reliable predictors of a faster time till death.[36, 45]

In our previous study on opioids and sedatives and time till death we demonstrated that time between the withdrawal of the different treatment entities is short.[17] In this study in 157 patients (65%) both VAM and MV were withdrawn at the very same time. This was only ethically possible because the majority of patients was already adequately sedated and treated with opioids before the WOLSM decision was made. This approach has several important advantages. Firstly, when life-sustaining measures are stopped at once, it is almost certain that the patient will die within 4 hours (±90% of patients). For families this is very reliable and hence important information.[15] Secondly when the patient dies very quickly after cessation of life support, families realize how depended the patient had become on all supportive measures and thereby the acceptance of the withdrawal decision might be facilitated. For understanding the Dutch values, it is very important to

note that the Dutch general public is strongly against continuing treatment when no cure or improvement is to be expected and that they are, with regard to end-of-life decisions often (even) more progressive than Dutch medical specialist.[38]
Severity of suffering in dying ICU patients can be formulated as a function of pain, discomfort, anxiety, fear, other forms of psychological distress and time. Pain, discomfort and psychological distress treatment should be optimal in end-of-life care, however the factor time is often not taken into account. Slowly withdrawing means often also slowly dying. In our population the imaginary area under the curve of a "time till death graph" is very small. When in that same population pain discomfort and distress are also adequately treated the total load of suffering is per definition low. We think that we certainly never should deliberately aim on hastening death, but unnecessarily postponing death might be ethically equally objectionable in this perspective.

STUDY LIMITATIONS

There are several limitations to this study. Due to the fact that patient inclusion was under the full responsibility of the research nurses, the study was fully dependent on their presence. The fact that 125 patients were missed for eligibility screening because of periods of their absence can be interpreted as a major drawback. However there are no arguments to think of how this practically might have led to patient selection or an in/exclusion bias, on the contrary just because the study was fully nurse driven, doctors involved were unaware of the study being done and can therefore not have been influenced by their presence or absence.
Although the two selected hospitals are complementary in background, size and patient categories and therefore are on average an adequate representation of the different non-academic ICUs in the Netherlands, a multi-center study would yield more homogeneous data and more reliable results. However, since the protocol is implemented nation-wide and medical educational programs are mostly centrally organized in a small country like the Netherlands, medical practices are very homogenous and differences are expected only to be subtle as already demonstrated by Spronk et al.[46]

Another limitation is that we started the observations just before the treatment was withdrawn (T0). Since most patients were already well sedated at T0, and we know that there is almost always a significant increase in opioids and sedatives in the last hours and that the highest dosages are always reported after treatment withdrawal, we think that describing the pre-withdrawal period will not yield additional information necessary for answering the questions of our study.[17, 32, 34] Since comfort of the patient is the most important goal after WOSLM, this study focused on patient signs and patient comfort alone. Of course evaluation of the family satisfaction has to be part of a follow-up study evaluating this protocol.

CONCLUSIONS

Dutch ICU patients in whom life-sustaining measures are withdrawn are relatively old and are severely ill. These patients do not seem to benefit medically from ICU treatment; therefore continuation of invasive ICU therapy does not seem to be in proportion. Most decisions for WOLSM are made in a multidisciplinary setting and are based on the disproportionateness of the treatment. Opioids and sedatives are widely used and dosages increase with a significant amount during the process of WOLSM, dosages are however comparable with the dose ranges previous observed by others and do not contribute to a shorter time till death. Patients in Dutch ICU's die rapidly, resulting in a dignified death with a low burden of suffering and little signs of discomfort. Further research is required to evaluate family satisfaction with this protocol.

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5 Hastening death due to administration of sedatives and opioids after withdrawal of life-sustaining measures.

EVEN IN THE ABSENCE OF DISCOMFORT?

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EDITORIAL

In a previous issue of the Journal, the Belgian Society of Intensive Care Medicine publishes a statement concerning "end-of-life" care in the intensive care.[1] They describe three principles. First, suffering should be avoided at all times. In addition they add an important statement to this first principle: A treatment considered to be without any meaningful perspective by the intensive care team will no longer bring benefit to the patient and might in addition even cause harm to the patient. Second, with the availability of modern organ support, most deaths in the intensive care unit (ICU) are preceded by a withhold/withdraw decision. And third, relatives should be informed of prognosis and end-of-life decisions at all times. We fully agree with these three generally well-accepted principles.

Furthermore they propose 10 general complementary principles that they believe should be adopted. Notably, the authors see no clear ethical distinction between withholding/withdrawing supportive therapy of vital systems and increasing the dose of sedatives and/or opioids in patients in whom further treatment is no longer considered beneficial (complementary principle 2). They also state that "shortening of the dying process with use of medication, *such as* sedatives and opioids may sometimes be appropriate, *even in the absence of discomfort*" (complementary principle 6) arguing that actions *like these* can actually improve the quality of dying and also can help relatives accompany their dying relative through the dying process (complementary principle 6). These actions should be regarded as not intended to end the life of the patient, but as a humane act to support the patient at the end of his/her life (complementary principle 9). The proposed principles apply to pediatric and adult patients (complementary principle 10) (italics from us).

Although the intention of these principles may be morally right—supporting dying patients and their loved ones and limiting and shortening suffering of a dying process, there is nevertheless a clear ethical dilemma in this. Is there a moral distinction between allowing a patient to die after withdrawal of life-sustaining measures and the deliberate termination of life? Is there a difference between allowing a patient to die following withdrawal of a life-support system on the one hand and shortening the dying process by increasing analgo-sedation in a

comfortable dying patient on life-support on the other hand? Does it make a difference when the doctor does not have the intention to kill the patient in this process? Many doctors hold the conviction that a ventilator-dependent patient is allowed to die after withdrawal of mechanical ventilation when further treatment is no longer appropriate. In this case the underlying condition of the patient or the organ failure causes the death of the patient. However, others regard the withdrawal of the ventilator or the vasopression as the immediate cause of death. Although the latter is emphasized by the fact that most of these patients die within 30 minutes following withdrawal, there is a moral obligation to anticipate on distressing symptoms for comfort during the dying process, but there is no moral obligation to hasten it.[2,3] Some patients, in whom mechanical ventilation is withdrawn, usually patients with catastrophic cerebral damage but with intact respiratory drive, will remain stable for hours or days. It is our moral obligation to anticipate on and treat distressing symptoms, not to deliberately end their lives. With adequate anticipation on death rattle, stridor, and dyspnea-associated distress, these patients can be extubated and kept comfortable easily till their death.[3] What is our intention when we decide to withdraw life-sustaining measures? Bosshard et al. reported that 66% of 3795 European physicians stated that they had the explicit intention of hastening death in cases in which they withdrew mechanical ventilation.[4]

In fact, withdrawal of mechanical ventilation in a ventilator-dependent patient is both causing death and allowing dying combined. Common sense notion of causation imply an equally causal role for doing and allowing in such a case.

Those who state that this is not the case defend a moral fiction.[5] If removing the ventilator causes the death of the patient, which is in most cases immediately[2], it is mistaken to suggest there is a moral difference between this action and deliberate termination of life by the administration of lethal medication, just on the basis that the withdrawal is seen as allowing and the administration of lethal medication as doing.[6] Both actions end suffering and incurable illness in a patient by the death of this patient. Death is the intended consequence of the action. There is no intensivist nor intensive care nurse who will be surprised that the patient dies within minutes after withdrawal of life-sustaining measures.

When the intended consequence of withdrawal of mechanical ventilation in a

ventilator-dependent patient with multiple organ failure is death within minutes, why is the administration of high-dose sedatives and opioids a problem? With or without the administration of high-dose sedatives and/or opioids, the patient dies shortly. We do not think that the problem with the statement lies in the administration of high-dose sedatives and/or opioids, but in the fact that it is recommended by the authors to administer them "even in the absence of discomfort". The action is then intended as deliberate termination of life without the consent of the patient. This is illegal, even in Belgium. Intensivists should follow the statements in the law regarding deliberate termination of life (euthanasia), and this is for good reason. In this light we do not see the rationale of this complementary principle. Why should we do an intervention that is against the law? Furthermore, there is no need to do this. In most cases the patient is not suffering, he/she is in the dying-process and will die within a short time period. We see no rationale to shorten this, in most cases, already short dying process in the absence of suffering. The authors (complementary principle 8) state that an individual's dignity must always remain a priority. In this context we see prolongation of disproportionate use of ICU resources (eg, in patients without any prospect of survival outside the ICU) as violation of an individual's dignity.

Deliberate termination of life without request of the patient is forbidden in both the Netherlands and Belgium. When such a case would come to court, judges could only see this as a criminal deviation of good clinical practice in palliative care.[7] Another troublesome part in the sixth principle is the addition "such as". The authors mention analgesics and sedatives, but what other kinds of medication would be applicable? There is an ongoing discussion if neuromuscular blockers have a place in palliative care, especially in pediatric end-of-life care.[8,9] We think administration of neuromuscular blockers will also be judged as deliberate termination of life without request of the patient as they end life immediately by causing paralysis. They only have a place in voluntary euthanasia. Administration of neuromuscular blockers is defended as means to relieve the suffering of parents in case their dying newborn lies gasping in their arms.[10] This forms a troublesome part of the whole discussion on end-of-life care in pediatrics and neonatology. The Dutch Groningen protocol of deliberate termination of life in newborns has given rise to heated debates in the international medical, ethical and societal

communities. In this line, causing general paralysis with neuromuscular blockers as part of "normal" palliative care will not easily be accepted.

In conclusion, we think the authors provide us a practical statement with workable principles, with the exception of the sixth complementary principle in which they state that it is appropriate to administer sedatives and opioids (and other medication?) in the absence of discomfort of the patient. With this principle the authors shoot themselves in the foot and could hurt the feelings of many colleagues in other European countries. With such a principle they will maneuver themselves in the same position as the authors of the Groningen protocol of deliberate termination of life of severely handicapped newborns.[11] Moreover they motivate colleagues to deliberately disobey the law, with the risk of lawsuit and subsequent conviction. And that is outside the commonly well-accepted principles of the highly sensitive position of end-of-life care in which society has an important judgmental voice.

Physicians and nurses have the moral obligation to relieve suffering, but they do not have the moral obligation to do so by shortening life. They should have the knowledge to anticipate on distressing symptoms that could occur after withdrawal of life-sustaining measures. In this perspective high-dose sedatives and opioids are only indicated in end-of-life care in acute situations as pulmonary hemorrhage or choking. Increasing the doses of analgo-sedation to shorten the dying process, especially when the patient is already comfortable, should not have a place in end-of-life care on the ICU.

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SECTION II

6

ETHICS

Ethical and practical considerations concerning perimortem sperm procurement in a severe neurologically damaged patient and the apparent discrepancy in validation of proxy consent in various postmortem procedures

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Abstract

Introduction
Although sperm procurement and preservation has been become commonplace in situations in which infertility can be easily foreseen, peri- or postmortem sperm procurement for reproductive use in unexpected coma or death, is not generally accepted. There are no laws and regulations for this kind of interventions in all countries and they may also differ from country to country. Intensive care specialists can be confronted with a request for peri- or postmortem sperm procurement, while not being aware of the country specific provisions.

Case description
A young male patient who suffered 17L blood loss and half an hour of cardiopulmonary resuscitation was admitted to an university hospital for an ill understood unstoppable abdominal bleed. After rapid deterioration of the neurological situation, due to severe post-anoxic damage, the decision was made to withdraw life-sustaining treatment. At that moment the partner of the patient asked for perimortem sperm procurement, which was denied, based on the ethical reasoning that consent of the man

involved was lacking. Retrospectively the decision was right according to Dutch regulations, however with more time for elaborate ethical reasoning, the decision outcome, without the awareness of an existing prohibition, also could have been different.

Conclusions
Guidelines and laws for peri- or post-mortem sperm procurement differ from country to country, so any intensive care specialist should have knowledge from the latest legislation for this specific subject in his/her country. An overview is provided. A decision based on ethical reasoning may appear satisfying, but can unfortunately be in full contrast with the existing laws.

INTRODUCTION

The first successful retrieval of sperm from a brain dead patient was reported in 1980[1]. In 1995 the first semen collection by rectal electro-ejaculation in a brain-dead patient was described and conception from perimortem sperm procurement (PMSP) was brought under the attention of the general public in the United Kingdom by Diane Blood[2-4]. Another milestone case was the Parpalaix case in France, where as a result the French Center for the Study and Preservation of Human Sperm petitioned the courts for a full ban on posthumous insemination.[5] In the United States, Gaby Vernoff was the first to conceive with intracytoplasmic sperm injection (ICSI) after the death of her husband.[6] Ever since, there has worldwide been an increasing interest in PMSP. Paradoxically, in a recent study of

8 years of PMSP in Israel, in none of the cases in which permission for PMSP was granted, the sperm was eventually requested for fertilization use.[7]
In other cases, the conclusion was often drawn that reproduction by means of PMSP was, for several different reasons, not ethically justified. In some countries therefore laws now prohibit PMSP under all circumstances, whereas other countries designed special laws for these cases, while other countries still lack legal provisions for procedures like PMSP.[8] Intensive care specialists are rarely confronted with this ethical dilemma; accordingly intensive care literature on this subject is scarce. In this article we describe a case of a severe neurologically damaged ICU patient, who was registered as a tissue and organ donor, in which a request on PMSP was denied.

Case description

A 30-year-old male was brought to the emergency department of a secondary hospital after a sudden collapse. Ultrasound of the abdomen showed free fluid with the density of fresh blood. The patient was transferred to the operation theatre for laparotomy. During surgery, he suffered massive blood loss and a 30-minute resuscitation procedure was necessary to regain circulation. After circulation was regained, the patient was transferred to our university hospital. Unfortunately the neurologic situation of the patient deteriorated rapidly on the third day.
The results of the Somato Sensory Evoked Potentials, implicated a potentially very bad prognosis, and were communicated to the mother of their 2-year-old son, who then asked if it would be possible to procure sperm from her partner to secure the possibility of a second child from this man.
After consultation of a clinical ethicist the decision was made not to facilitate sperm procurement. The paramount reason was that written consent of the patient for sperm collection was lacking and consent could not be presumed.
In this phase the physician is required to consult the Dutch donor registry to find out if the patient was registered as an organ and/or tissue donor, which he was. Since the family did understand the poor prognosis they agreed with withdrawal of the mechanical ventilation and supported the wish of the patient to donate his organs and tissues. After circulatory death, both kidneys and the heart valves were used for transplantation.

DISCUSSION

Although the decision not to proceed with PMSP was legally correct, as gamete harvesting for cryopreservation in both man and women is only justified under Dutch law with a written patient consent, as we learned by analyzing this case, the question is whether the original decision made, can also be ethically justified? In this case we do have doubts.

There are six entries for the discussion:

1: COMMONLY DESCRIBED REASONS FOR REFUSAL OF PMSP

In the past, several cases have been described in which the request for PMSP, or the authorization for the use of the procured sperm, was turned down.[9-12] The reasons that have been given were: The lack of proof of an established relationship, a mother or parents who wanted sperm from the dead son, lack of agreement between the relatives of both partners, the deceased patient didn't want children when alive and finally, the lack of a written consent. In our case only the last reason applies. When a request for PMSP is denied, an often used argument is, that the person who should be responsible for the decision never can be certain about the fact if the patient would have agreed with it given the circumstances.[13, 14] Therefore in the Netherlands and for example also in the UK gamete procurement in a comatose or peri-mortem patient is only possible with a signed consent of the patient. The paradoxical outcome of such legislation is however, that since almost nobody will sign such an advance directive, gamete procurement becomes practically impossible in any unanticipated coma, vegetative state or (brain) death.

2: THE STABILITY OF THE RELATION BETWEEN THE PATIENT AND HIS PARTNER

The patient and his partner had a long lasting, officially registered relationship with rights that equals that of a married couple in the Netherlands. They

were parents of a 2-year-old son and a possible recent miscarriage proved that the family was not regarded as complete yet. Proxies from both sides of the family confirmed the wish for another child in this relationship and they all declared that the man would have agreed with sperm procurement if he had had the possibility to do so, because, as they stated: "It would have been in his line of thinking." Based on a protocol proposed by Batzer et al. and on a dichotomous key-approach for PMSP decision-making, there would have been no reason why PMSP should have been refused in our case.[15, 16] The steps 1, 2 and 4 of this key-approach are essential; there is a proven established relationship, there is evidence that the deceased person wanted to have children and there are witnesses other than the requesting person that can confirm that the deceased person possibly could have agreed with the procedure. In any other case there seems to be no ethical justification for PMSP.

3: A SPOUSE CAN LEGALLY AUTHORIZE ORGAN PROCUREMENT AND AUTOPSY BUT NOT SPERM PROCUREMENT

The most important reason why the clinical ethicist involved in this case advised against sperm procurement was, that it may be ethically questionable to assume that a man who wants a complete family, that still wants without him being present. However it seems illogical to us to enable post-mortem organ procurement or autopsy without patient consent and at the same time deny the request for sperm procurement.

In the Netherlands proxies are allowed to decide whether or not a patient will become an organ donor, if the patient did not leave an advanced directive, or is not registered in the organ donor registry. Likewise proxies are entitled to approve post mortem autopsy. It is important to realize that autopsy is a highly invasive act, harming the bodily integrity, which is in no way serving the interests of the patient. Any kind of tissue can legally be collected during autopsy (even more ethically sensitive tissues like testicular tissue) and stored thereafter and used for research for years, without consent of the patient. These rights are based on the presumption that the proxies do have a reliable idea about the religious-, moral- or political thinking of the patient in question and are generally accepted because it facilitates

organ donation in individuals who are not registered in a donor registry. Proxy consent for organ donation or autopsy is regarded as altruistic for third parties and in this way serving society or science as a whole. However, when proxies are supposed to be capable of making a "well judged" decision for a patient concerning organ donation or other post mortem interference with the body, why then do others state that a partner wouldn't be able to make a balanced decision about PMSP? Some argue that the possibility of conflict of interest which would interfere with the proxy's capacity to provide adequate "substituted judgment" is accordingly much greater than for organ donation. This is however not supported by evidence and a conflict of interest is certainly not necessarily present in these situations.

We wonder, which subject will be more discussed within relationships of young couples: organ donation or family planning? PMSP in itself shall never be discussed, but partners will definitely have a reliable idea of how the other partner thinks about reproduction or family planning.

4: ORGAN DONATION IS CONSIDERED ALTRUISTIC, PMSP SELFISH

Some authors consider asking for PMSP as an act of selfishness, as compared with the altruistic character of organ donation. The presumption that organ donation is without "reward" and therefore not selfish, is questionable, as there is an undeniable psychological benefit that is inextricable connected with altruistic actions and "good deeds". This positive feeling obtained after making a difficult choice, is psychologically to be regarded as "reward". Furthermore it is assumed that when organ donation is made possible, "society" will benefit. However, it is not society, but a few "lucky" individuals, and often only just one or two, due to the disappointing organ quality after circulatory death. When PMSP would have been made possible and the partner of our patient had become pregnant, then there were also two individuals that would have taken benefit; the partner that finds hope in new life that is deeply connected with the man she lost and her son that get's a little baby-brother or -sister.

5: TIMING OF SPERM PROCUREMENT

It is generally recognized that procurement before circulatory death is preferred over procurement after circulatory death, because after death the harvesting methods are limited and invasive. Moreover procurement is only successful when performed in the first 24-36 hours after death. The patient's partner asked for the PMSP on the right moment from another point of view, (i.e. before withdrawal of life sustaining treatment, before the official moment of death) because as formulated by White, "when the husband is in a coma or in a persistent vegetative state and they are still married, the wife cannot remarry and cannot have a child legally with another man. …If the husband is dead though, they are not married anymore and the wife is free to marry and legally have children with somebody else, making PMSP not permissible with wife's consent alone".[17] Based on this point of view, we would have at least had an argument to procure and preserve sperm as was also suggested by the wife of the patient in the case described by Moser.[11] The discussion whether or not it might be used, would then follow later as in the "Blood" case.[3] In this perspective it is important to realize that in countries where PMSP is allowed, a 6 to 12 month period for bereavement and reflection is mandatory, before the first attempt for fertilization is initiated. The fact that the High Court in the UK, referring to the European law for unimpeded exchange of medical care, made the export of the sperm in the above-mentioned "Blood"case possible, potentially provides an escape route for future cases in European countries where PMSP is not allowed or restricted. Retrospectively, we could have brought our patient, before withdrawal of treatment, to Belgium also, to make PMSP possible there. Unfortunately, there was at that time no overview readily available of the possibilities and regulations in the various European countries. Therefore we analyzed all available literature on PMSP laws and regulations in various countries and summarized these results in Table 1.

Although this overview could be of assistance in a case of PMSP request, detailed knowledge of the own situation is still of the utmost importance, therefore most doctors in Europe shall consult the juridical department of their hospital for further guidance, when in doubt about the applicability of legislation or unclarity of the rules in such a case.

6: THE INTEREST OF THE CHILD TO BE

A last argument sometimes posted against PMSP is that we are not informed about the potential negative effects on the development of the child to be. Although we do agree that the interest of the child always should be guarded, the fact is, that there is no clear evidence available that a child raised in a loving but different system than a mother-father system, is less happy, stable or successful than any other child.[20]

Table 1. Overview of rules and legislations concerning perimortem sperm procurement and use for fertilisation in different countries in and outside Europe [5, 8, 11, 15, 18, 19]

	Prohibited by legislation or guidelines	Written consent obligatory	No written consent obligatory	Not defined in guidelines or legislation
Australia			#	+
Belgium			+	+
Canada	+			
Denmark	+			
Estonia	*			
Czech Republic		+		
France	+			
Germany	+			
Hungary	+			
Ireland				+
Israel			#	+
Italy				+
Japan				+
Latvia				+
Lithuania				+
Malta				+
Netherlands	+			
Norway	+			
Poland				+
Portugal				+
Slovakia				+
Slovenia	+			
Sweden	+			
United Kingdom		+		
United States			+	+

* Sperm can only be obtained and/or used till maximally one month after death and only when assisted reproduction was already initiated before death.
# Only possible by court order, no special law

CONCLUSION

Although a request for PMSP will remain a rare event on the ICU, intensive care specialists should be aware of the practical and legal issues involved, since the decision whether or not to proceed into PMSP can only be taken in a relatively short time-window. Different countries have different laws and regulations in relation to PMSP and each intensive care specialist should have an idea about the country specific regulations on this subject. Cross-border European medical care may provide a potential escape route for patients in countries where PMSP and/or cryopreservation are not allowed.

The woman in our case had the right and the possibility to give away organs and tissue, to give permission for autopsy and to become a single mother by insemination of sperm of an anonymous donor, but not the right to become a mother by PMSP from her own legal sexual partner. The question remains whether this is a logical ethical decision or just a flaw in law and reasoning?

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7

ETHICS

Obtaining consent for organ donation from a competent ICU patient who does not want to live anymore and who is dependent on life-sustaining treatment; ethically feasible?

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Abstract

We anticipate a further decline of patients that eventually will become brain dead. The ICU is considered a last resort for patients with severe and multiple organ dysfunction. Patients with primary CNS failure constitute the largest group of patients in which life-sustaining treatment is withdrawn. Almost all these patients are unconscious at the moment physicians decide to withhold and withdraw life-sustaining measures. Sometimes, however competent ICU patients state that they do not want to live anymore because of the severity of their illness or the poor prognosis and ask for withdrawal of life-sustaining measures like mechanical ventilation. Do we consider the unconscious patient as potential organ donor before withdrawal of mechanical ventilation? This is paradoxically rare in the case of the conscious ICU patient. Is it practically possible and ethically feasible to obtain consent for organ donation from this group of patients?

INTRODUCTION

Since the first observational descriptions of brain dead patients by French and German neurologists in the late 1950's, many thousands of artificially ventilated patients in intensive care units worldwide have been declared dead after the determination of irreversible failure of determined brain functions, and in almost all cases in favour of organ donation for transplantation.[1,2] Brain death has always been a rare outcome of intensive care treatment of patients with severe brain damage due to traumatic brain injury, or severe forms of stroke (subarachnoid haemorrhage (SAH) and intracerebral haemorrhage). Recently it was demonstrated that the percentage contribution of brain dead organ donations to the total of organ donations has been decreasing significantly in the Netherlands in the past 15 years.[3] Due to changes in demographics, increased traffic safety, improved treatments like early coiling of cerebral aneurysms and legislation prohibiting smoking (an important risk factor for SAH) in public places we anticipate a further decline of patients that eventually will become brain dead.[3] Considering the fact that the brain dead donor is the ideal organ donor, since only when brain dead is diagnosed there's the possibility to procure the heart and the organs will generally have a better quality, an anticipated decline in brain dead donors means a further setback for transplantation medicine. Therefore many initiatives are developed and deployed in order to decrease the gap between patients awaiting an organ and the number of actual organ donors. These initiatives include a better

organization of donor care on a national, regional and hospital level inspired by the Spanish model or a change in the system of consent.[4] Several European countries like Spain, France, Belgium, Austria and Sweden adapted a form of presumed consent or opt-out.[5] Some North European countries like the UK, Denmark, Germany and the Netherlands have considered a system of opt-out but eventually choose to maintain their current system of opt-in.[6,7] Taking into account the diminishing supply and the growing need for organ transplantation, one has to pursue and analyse every potential area of improvement.

The ICU is considered a last resort for many patients with severe and multiple organ dysfunction. Therefore it is the hospital department with the highest mortality rate. Approximately 15% of all admitted patients die on a mixed intensive care unit. End of life care is considered a vital part of the ICU. The majority of the patients that die on the ICU, die as a result of withholding or withdrawing life sustaining treatment.[8] According to a paper by Sprung and colleagues the primary reasons for the end of life decisions are unresponsiveness to therapy (no diagnosis reported in the paper), neurological reasons, chronic disease and multi-organ failure.[9] In a recent paper, Verkade and colleagues studied the incidence of withdrawal of life-sustaining treatment in various group of patients in a single centre, mixed ICU in the Netherlands.[10] Patients with primary brain failure constituted the largest group of patients (86/174, 49.4%) in which life sustaining treatment was withdrawn. Specifically this group of patients is most likely to be eligible to eventually donate organs after death, but only a few will eventually reach the state of brain death. For this reason donation of organs after circulatory death is increasingly considered. In the Netherlands the number of donations after circulatory death increased from 118 patients in the period between 1995-1999 to 453 patients in the period 2005-2009 according the annual reports of the Dutch Transplant Foundation.[3,11] At the same time the amount of brain dead organ donors is significantly declining. Nowadays in many countries, organ donation after circulatory death forms an important source for kidney, liver and lung transplantation. All these patients are deeply unconscious or deeply sedated at the moment life-sustaining measures are withdrawn.[12]

However sometimes competent ICU patients, who are dependent on intensive care measures like mechanical ventilation, state that they do not want to live

anymore because of the severity of their illness and the poor prognosis and ask for withdrawal of life-sustaining measures in order to die.[13] In most cases in the Netherlands, the autonomy of these patients is respected and life-sustaining measures are then indeed withdrawn. Recently we described two conscious patients who died on the ICU after they asked for withdrawal of life sustaining treatment.[13] In which way do they differ, besides the level of consciousness, from the other patients in which we withdraw treatment and in which we consider organ donation? Why do we not consider these conscious patients as potential organ donors before withdrawal of mechanical ventilation?

There is some experience with organ donation after planned deliberate termination of life (euthanasia) in Belgium,[14,15] but we are not aware of documented cases in which ICU physicians ask patients, before withdrawal of life-sustaining treatment, if they are willing to donate their organs after death. In the light of the scarcity of organ donors, perhaps we have to reconsider this point of view. The aim of this paper is to discuss the pros and cons of such a change in end-of-life care, focussing on the current ethics and the practical feasibility.

SCENARIOS

The following two cases have been selected to engage the discussion of ethics.

Patient A, a 45-year-old electrician, is admitted to the general ICU after a fall from a ladder. The fall resulted in fractures of three cervical and one lumbar vertebra, and mild traumatic head injury. During his stay on the ICU he shows no improvements of his tetraplegic status. In the weeks thereafter it is impossible to wean the patient from the mechanical ventilator. He eventually regains full consciousness and can communicate with eye blinking and later by lip reading. He is informed about his clinical situation. The patient is well aware of his situation and the unavoidable restrictions for his future daily activities. Several weeks after admission, he repeatedly expresses a clear wish to have life-sustaining treatment withdrawn and asks the ICU team to take him off the mechanical ventilator. After several deliberations between family members, various physicians, nurses and a clinical ethicist we

agreed to offer him, according to his will, deep palliative sedation, followed by withdrawal of life-sustaining treatment. After initiation of intravenous administration of midazolam the patient enters a deep sleep. Inotropic support and mechanical ventilation were withdrawn. After 15 minutes the patient died peacefully in the presence of his family.

Patient B, a 45-year-old business administrator, is admitted to the ICU with severe neurological injury after a high-speed road traffic accident. A CT-scan shows several subdural hematomas, a skull fracture and compression of the brainstem. Because of the low GCS score the patient is intubated and connected to a mechanical ventilator. When the patient is neurologically assessed by a neurosurgeon he has a Glasgow Coma Score of E1M1V1, an absent pupil and corneal reflexes. However because of some intact brainstem reflexes the patient is not considered to be brain dead. After several weeks of ICU treatment, the patient shows no neurological improvement. In a multidisciplinary meeting it is decided to withdraw life-sustaining treatment based on the poor prognosis of the patient. When discussing this decision with the family, the treating physician also mentions the option of organ donation. Because the patient is not registered in the national donor register, the relatives of the patient are mandated by law to make the decision regarding organ donation. After much discussion they agree with organ donation according to the protocol of donation after circulatory death (DCD). In the presence of the family the mechanical ventilator and other life sustaining therapy are withdrawn. The patient dies after 30 minutes of cardiopulmonary arrest. After the mandatory 5-minute "no-touch" period the patient is transferred to the operation theatre for organ retrieval.

DISCUSSION

When comparing both scenarios there are many similarities but also some important differences. Both patients die as result of an action, namely the withdrawal of life-sustaining measures, which is done by the physician after multidisciplinary deliberation.[16] While in the first scenario the patient explicitly asks for the withdrawal of life-sustaining measures in order to die, in the latter case the decision is made by a multidisciplinary group of physicians and other health care workers. Both patients were suitable for organ transplantation after death but only the

second patient donated his organs after the physicians asked consent of the family. The other, conscious, patient could have decided if he wanted to donate one or more organs, but was never approached with the question concerning organ donation. Essential in the decision process surrounding the withdrawal of life sustaining treatment in patients that are awake, as we discussed in detail in our previous paper, is respect for the autonomy of the patient. Dutch caregivers have to respect, by law (medical treatment agreement act (Wet Geneeskundige Behandelings Overeenkomst)), the wishes of the patient if they are understandable and within the accepted possibilities of medical care.[17,18] This also implies that a doctor is not allowed to start or continue a treatment that is not wanted by the patient. This is clearly stated in article 450 of the above mentioned law: "For all actions and treatments within the treatment contract the explicit approval of the patient is needed". So there has to be no doubt concerning the cognitive functioning and competency of the patient.[13] According to Beauchamp and Childress an autonomous action should be made by someone (1) who acts intentionally, (2) with understanding of the consequences at hand, and (3) without controlling influences that determine their action.[19] In the first case the decision to withdraw life-sustaining therapy is made by the treating physician after the explicit request of the patient. The patient made this request with the knowledge that the withdrawal of the mechanical ventilator and inotropic medication will result in a certain death. He acted intentionally with the limited means of communication he had at his disposal and family or friends did not influence his actions. Nevertheless he was not asked if he wanted to use the option of donating organs after his death.

The ethical basis of deciding to donate organs after death is that it is ideally an autonomous choice, made by the individual when he or she was healthy of mind. The central donor registry, which is an essential tool with regard to organ donation in the Netherlands, is based on this same respect for patient autonomy.[20] When an individual decides that he or she wants to donate organs or tissues after death, then this is effectuated, if possible, in almost all cases. In the case of no registration in the donor registry, the relatives of the patient are approached to consider permission for organ removal after death of the patient, as is described in the second scenario.

In the Netherlands, individuals can ask a physician for withdrawal of treatment, but also for intentional termination of life. This presupposes absolute voluntariness (seen from the patient) and a deliberate act (seen from the physician). It excludes every form of intentional, active, direct, non-voluntary termination of life. In the Dutch "Termination of Life on Request and Assisted Suicide Act", the requirements of due care are described.[21]

This above mentioned Act requires that the physician:

- Holds the conviction that the request by the patient is voluntary and well considered
- Holds the conviction that the patient's suffering is lasting and unbearable
- Has informed the patient about the situation and about the prospects
- Holds the conviction that there is no other reasonable alternative in the light of the patient's situation
- Has consulted at least one other independent physician who must have seen the patient and given a written opinion on the due care criteria
- Has terminated a patient's life or provided assisted suicide with due medical care and attention

The same requirements, with exception of the last, are applicable for the scenario in which a competent patient on the ICU ask for termination of mechanical ventilation and other life sustaining measures. In such a situation, taking the above-mentioned requirements in consideration, the request has to be taken seriously. If approved, the patient is brought to sleep with sedatives after which mechanical ventilation is withdrawn and the patient dies. Euthanasia (deliberate termination of life after injection of euthanatica) is very rare in the ICU setting in the Netherlands.[22] Withdrawal of life-sustaining measures is however common.[8,9,12]

Why then do we not just ask patients before withdrawal of mechanical ventilation whether they are willing to donate their organs? There are four arguments that can explain why the patient is not confronted with the donation request:

1. The patient is not recognised as a potential donor
2. There is fear of creating a conflict of interest
3. There is fear of creating a self-fulfilling prophecy
4. There is fear of harming the doctor-patient relation

The most obvious reason why the patient is not approached is probably because he's simply not recognized as a potential donor. In the, often emotional, process of handling the patient's request of withdrawing treatment, the focus of the medical team will primarily be on the legal and ethical issues involved with that process and therefore the possibility of organ donation will just not enter their mind in that stage. Since there is, until now, no documented experience with organ donation in these situations, the likelihood that this way of thinking will change in short term is not great, thereby creating inevitably a vicious circle.
Some scholars will reason that a conflict of interest will arise in such a situation, but we do consider this a moral fiction. The autonomous patient asks voluntarily for termination of life (as in the Belgium cases of organ donation described by Ysebaert et al.[14]) or termination of life sustaining measures. It is important to realize that it is not the physician who initiated this, but the patient himself. The physician follows the voluntary and well-considered request. What if the patient asks, besides the request for termination of life or withdrawal of mechanical ventilation, for organ donation after death? Do we have reasons to reject this? We cannot conclude this. We therefore argue that there are no moral objections for asking the patient for organ donation if the request for life termination or withdrawal of ventilation is granted. A conflict of interest can only then arise when the physician himself initiates the process of considering withdrawing of life support for the patient. Although we certainly appreciate an open patient/physician relationship in which all aspects of treatment can be discussed, the initiative for withdrawing treatment in a conscious patient (in analogy with euthanasia) should always come from the patient alone. A "helping hand" in this decision process is indeed, in cases like this, the key to an unwanted conflict of interest.

Another point of concern that some will mention is the introduction of a potential self-fulfilling prophecy. At this moment when this patient category is not yet

recognised as a potential donor this risk is negligible. However, when this changes, the general public may be inclined to think that physicians would be tempted to be deliberately pessimistic about the patient's prognosis to enhance the patient change of request for withdrawal of treatment. Although this is a non-rational factor, it is unfortunately in concurrence with the documented fear of the general public that doctors will be tempted to prematurely declare death in order to procure organs.[23] Distrust of society and henceforth a negative discussion in the lay press, although non-rational, should be regarded as a real threat for the proposed scenario. In fact, all the arguments proposed in this paper are within the law. Moreover the corner stone for this proposal is that the patient himself must first ask for treatment withdrawal and a second (independent) physician must approve. Therefore it is almost impossible to create a self-fulfilling prophecy in this scenario. The proposed scenario is in fact fully in line with, the generally well supported intention of the Organ Donation Act in the Netherlands; giving everyone the chance to donate his or her organs after dying.[24]

A last argument that may be put against this proposal is the fact that the patient himself may experience pressure in the choice he has to make. Some will argue that the patient will be aware of the fact that "yes" to the donation question is the desired answer and since the patient is dependent on his physician to withdraw treatment and the provision of care in that process, the patient may feel forced to give an answer that pleases the caregiver, even though it may be in contradiction with his personal values. However, a patient that dares to ask his treating physician to stop a treatment that has been supported by his physician shows already a high level of self-differentiation. The fact that both doctor and patient have been able to discuss such a delicate matter together gives proof of a well-formed doctor-patient relationship. Therefore we think it's highly unlikely that a well self-differentiated patient with a good doctor-patient relation will be tempted to choose something that is against his own principles or values in such a situation. Organ donation after circulatory death is legally and ethically accepted in many Western countries, taking the dead donor rule in consideration. The dead donor rule is the ethical and legal rule that requires that donors are not to be killed to obtain their organs.[25] The dead donor rule is vital for the donation and transplantation system and helps to maintain the public trust in organ

donation after death. After five minutes of circulatory arrest with no ventilation the patient is considered dead and organ removal can take place. The situation is equal in cases where an unconscious patient with devastating neurological damage dies after withdrawal of mechanical ventilation, as in cases where a sedated patient, who was conscious before sedation, dies after withdrawal of mechanical ventilation. Both patients are then equal and suitable for organ donation. For this reason we see no obstacles for organ donation in the described context.

CONCLUSIONS

In a medical community in which withdrawal of life-sustaining measures in unconscious and in conscious ICU patients is accepted, where organ donation after death is common practice, and in which there is a shortage of organs for transplantation, there can be no moral objection to ask certain conscious ICU patients to donate their organs after death. Although withdrawal of mechanical ventilation on request of the patient on the ICU is rare and therefore the number of organs that come available is limited, it is still well worth considering. We argue that there are no valid moral or legal objections against it; it is ethically feasible and practically possible to ask the patients for organ donation after death.

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8

ETHICS

Determination of brain death in organ donation; is an EEG necessary?

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Abstract

The determination of brain death is a requirement for multi-organ donation of a ventilated patient in the ICU. The criteria for brain death however differ internationally. In some countries brain stem death is equivalent to brain death. In other countries, including the Netherlands, to establish brain stem death an EEG must also be conducted to rule out cortex activity, according to the criteria for 'completely brain dead'. This however does not prove complete failure of all brain function since in an EEG the subcortical brain is not examined. According to the Health Council of the Netherlands, brain death is ruled out by rest activity in the cortex and not by persistent subcortical activity. This is conceptually incorrect. The criteria for brain stem death better reflects the practice than the criteria for complete brain death. Conducting an EEG should therefore no longer be required to establish brain death, as seen in other countries.

INTRODUCTION

The determination of brain death is a requirement for multi-organ donation. For a ventilated patient in the ICU with traumatic brain damage, brain death is not necessarily an outcome. Doctors and the patient's loved ones are less prepared to wait for the time consuming procedure to confirm brain death. They therefore may choose sooner to withhold treatment and commence the potential donation process after death is confirmed by circulatory arrest and not after the establishment of brain death.[1] The number of brain dead patients is decreasing as a result of primary prevention – thereby less frequent and less severe brain haemorrhage and less severe car accidents – and better treatment of patients with cerebral vascular accidents such as subarachnoid haemorrhage and traumatic brain injury. It is important to clearly define 'brain dead', particularly in the context of potential organ transplantation in this group of patients. When discussing brain death, two concepts are distinguished: 'brain stem death' and 'complete brain death'. In brain stem death, the brain stem and the medulla oblongata have stopped functioning. In 'complete brain death', besides brain stem function failure there must also be failure of the cerebral cortex.

In the Netherlands, the concept of 'complete brain death' is practiced. This is stipulated and is therefore legally binding, as are the criteria for brain death by the Health Council of the Netherlands.[2] In order to establish complete brain death, an iso-electric EEG – an EEG where no activity of the cerebral cortex can

be detected – is required, despite the fact that various experts in the last forty years have raised questions about the use of this requirement.[3-8] In many countries, including half of the European countries, the EEG is an inherent part of the establishment of brain death in the context of organ donation procedures.[9] In some countries, an EEG is only performed to confirm brain stem death and in other countries, including the United States, an iso-electric EEG not required at all. In this article we give arguments for the use of the concept 'brain stem death' instead of 'complete brain death' in the case of organ donation procedures.

BRAIN STEM DEATH VERSUS COMPLETE BRAIN DEATH

In this article we will argue that the concept 'brain stem death' is ethically and conceptually acceptable and that although the concept 'complete brain death' presumes completeness it can in fact never be fully attained. Both concepts will be discussed first separately to make this clear.

BRAIN STEM DEATH

In brain stem death there is complete failure of brain stem function and the medulla oblongata. In some countries, clinical irreversible failure of brain stem function is the only evidence required in order to establish brain stem death. The evidence consists of observations from neurological examination, such as the absence of both brain stem reflexes and spontaneous breathing. The argument for brain stem death as criteria for the end of the life of a person is that the brain can only function in combination with the brain stem and the medulla oblongata. Irreversible loss of the brain stem function effectively makes further brain activity impossible. The function of the brain as a whole and, thereby also consciousness, is then entirely lost and recovery in this case is out of the question. For confirming brain stem death, the presence or absence of electrical activity in the cerebral cortex is irrelevant. An intact, functional brain stem is a 'conditio sine qua non' for intact consciousness. In many countries, this reasoning provides indisputable evidence of brain stem death on the basis of clinical tests, therefore without the need to perform an EEG to conclusively pronounce a patient dead and possibly proceed to organ donation.[2,10]

COMPLETE BRAIN DEATH

By complete brain death, the complete biological death of the brain as an integrated organ is assumed to be established. Determining complete brain death is based on 3 pillars: **a)** preconditions such as the absence of hypothermia and intoxication which may explain the clinical presentation; **b)** neurological examination of the brain stem reflexes and measurement of the depth of the coma; **c)** supplementary examination with an EEG and an apnea test.

In neurological examination one must be certain that there are no confounding factors that affect the patient's clinical condition such as residual effects of previously administered sedatives or metabolic disruptions. If, after examination, it is established that the patient in deep coma lacks brain stem reflexes including apnea, and the reason of such a state is known and conclusive, it can then be said that the patient does not have a chance to recover. There is therefore no reason to believe that conscious perception is possible for the patient.

Additional examination with an EEG is, in contrast to the determination of brain stem death, a fundamental procedure. The presence of electrical activity in the cerebral cortex is still a 'sign of life', even though there is indisputable evidence that the brain stem and medulla oblongata have permanently lost their function. Undoubtedly, the absence of electrical activity in the brain signifies death in a patient.

LIMITATIONS OF THE EEG

An understanding of the value and limitations of an EEG is of importance when considering the different concepts of brain death.

The surface EEG measures the activity of the neurons in the outermost layer of the cortex. Dendrites, which lie deeper in the cortex and sulci, are not reached. Consequently, the iso-electric EEG is not conclusive evidence that the cortex as a whole no longer functions or that above the level of the brain stem complete brain death has occurred. It is essential therefore to rule out electrical activity of the neurons in the deeper levels of the brain. The results of an EEG can in another way lead to drawing false conclusions. In a literature review, 147 patients were described as lacking brain stem reflex and spontaneous breathing, even though an EEG indicated cortical activity.[4] In spite of the best treatments, within a few days all patients went into cardiac arrest. The 16 patients however with brain

stem reflexes and spontaneous breathing but with an iso-electric EEG, stayed alive.[7] This has been also found in other studies of patients in a vegetative state – first described as 'apallic syndrome'.[11]

Residual activity on an EEG is repeatedly observed in patients with severe supratentorial brain injury with secondary brain stem impingement, and in patients with primary brain stem injury lacking brain stem reflexes.[4,7] Based on the observations in these patients, it would be expected that even with the presence of EEG activity there is a complete non-functional or "dead" brain stem.

The prognosis of a patient with brain stem death is unfavourable. Among the lay press, there is sometimes mention made of 'brain dead' patients who wake up. These messages are founded, without exception, on false interpretations of the current terminology and consensus criteria for brain stem death.[12,13]

There are no known cases of long-term survival after the determination of brain stem death. Even in Japan, where patients continue to be given long-term treatment in the ICU even after the determination of brain death, there are no known cases.[14] Until 2009, according to law, a patient in Japan is only considered brain dead if an organ transplant will be performed.

HOW COMPLETE IS BRAIN DEATH?

The reliable determination of complete brain death is, considering the above, not possible with an EEG. As previously mentioned, the EEG examination measures the outermost layers of the cerebral cortex and can therefore in no way prove that there is an absence of neuronal activity in all parts of the brain.

SUBCORTICAL ACTIVITY

In approximately 25% of the patients who are completely brain dead – that is, patients with no brain activity according to the EEG – it was found after further examination some brain function such as in the hypothalamus and the diencephalon was still intact.[15,16] In post mortem investigation of brain dead patients it has been shown that the subcortical parts of the brain, such as the hypothalamus, have been functional without showing residual activity on the EEG. Furthermore, indications have been found that parts of the subcortical brain were microscopically normal; disproving that the cells of these structures had died.[17]

Proponents of the 'complete brain dead' concept would need to argue why persistent cortex activity is important but persistent hypothalamic activity is not. In 1996 the Health Council of the Netherlands stated, 'the EEG is a necessary, supplementary examination because if all brain stem functions have failed, the functions of the cerebral cortex evade clinical observation.' The council is aware that the lack of electrical activity in the EEG does not dismiss that cells or groups of cells in the deeper brain structures could still possess electrical activity or that in some patients the cells in the hypothalamus or the posterior pituitary could still be endocrine-active. The Council nevertheless takes the view that these symptoms are not related to the distinctive, higher functions of the human brain or its essential intermediary or support functions'.[3]

NEW INSIGHTS

In 2004 new research discovered that the hypothalamus is involved in much higher brain functions than previously believed. The researchers maintain that the concept 'complete brain death' is difficult to uphold if parts of the hypothalamus are still active.[18] Brain stem death according to current insights is not compatible with any form of consciousness or of even the slightest chance of recovery. It seems therefore incorrect in the case of patients without brain stem function but with some residual EEG activity in the cerebral cortex to not consider them 'brain dead'.[4, 19] Furthermore, this is inconsistent with the view that parts of the brain that release hormones or possibly play a role in higher brain functions are not considered in the interpretation of 'alive' or 'dead'.

PUBLIC OPINION

Consent for organ donation requires the confidence of a patient's loved ones in the ethical correctness of the determination of death. This applies particularly to patients in whom death would be determined under special circumstances, such as those ventilated and with intact blood circulation. This was again highlighted in the case of Carina Melchior in Århus, Denmark. This young woman, supposedly 'brain dead', woke up and recovered. Would this confidence decrease if the EEG no longer was used to make this determination? We do not think so. It is known from research that a patient's loved ones are largely convinced when they see

that during the examination of brain death by the doctor, the patient's breathing during the apnea test is absent and the patient is unresponsive to pain stimuli. These observations contribute more to this confidence than any supplementary examination, such as the EEG.[20] This can partly be explained by the limited understanding of the term 'brain dead' among laypeople.[21]

IMPLEMENTING CRITERIA FOR BRAIN STEM DEATH

We propose that, in the Netherlands, the concept 'brain stem death' be adhered to instead of the current concept of 'complete brain death'. This would have consequences in decisions regarding organ donation. Considering the care needed to determine all forms of brain death and the importance of preserving the confidence of patients and their loved ones, any changes in the current practice would need to be fully argued. Two essential issues would first need to be considered: **(a)** national consensus among medical colleges and **(b)** well-informed professionals and society, and in particular, a good understanding that changes in current practice are founded on medical insights and not on an underlying motive to create more organ donors.

CONCLUSION

Absence of activity on an EEG in combination with the cessation of brain stem reflexes and breathing confirm 'complete brain death'. Even though the criteria for brain death in the Netherlands is 'complete brain death', it can still not be stated with certainty that there is complete failure of all brain functions and neural activity in the brain. The presence of cortical activity from an EEG rules out complete brain death, but not persistent function of the hypothalamus. This is conceptually incorrect. The determination of 'brain stem death' would be better applied in practice than the determination of 'complete brain dead'. In the Netherlands, just as in other countries, the EEG should no longer be obligatory in determining brain death.

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SECTION III

9

"There are two
ways to be fooled.
One is to believe
what isn't true;
the other is to refuse to
believe what is true."

Søren Kierkegaard,
19th century
philosopher
and theologian

GENERAL DISCUSSION

The five questions considering death and end-of-life care ethics, related to intensive care medicine, described in the introduction of this thesis, have definitely been answered, however not each of these five answers is clearly and separately mentioned in each individual chapter. Therefore, the results of two or more articles have to be combined in order to come to a well-balanced conclusion.
Moreover, there are also some issues that weren't part of the initial study questions that nevertheless have become a small but interesting part of this thesis; like the amount of family involvement in the withdrawal decision-making process and the progression of severity of disease in patients in whom life-sustaining measures are withdrawn. These subjects and the answers to the initial study questions shall be discussed below.

INCIDENCES OF WITHDRAWAL OF LIFE SUSTAINING MEASURES IN THE ICU

Although the ETHICUS study, the prospective landmark study on withdrawal of life-sustaining measures and withholding of treatment in the ICU in Europe, in which unfortunately only one Dutch hospital participated, has revealed that the incidence of withdrawing of life-sustaining measures in the ICU is higher in Northern Europe (47 percent) than in Central- or Southern Europe, respectively 33.8 percent and 17.9 percent, no data about incidences of withdrawal on individual hospital level or even country level were published.[1]
This lack of clear country related incidence data, is probably one of the most important factors that made Fumis and Deheinzelin mistakenly conclude that Northern European intensive care specialists are more reluctant in withdrawing life-sustaining measures on the ICU than their American colleagues.[2] In the letter to the editor presented as paragraph 3-2, we prove that they are wrong in their conclusions especially concerning the situation in the Netherlands.
The first article ever published on withdrawing life-sustaining measures and withholding in the Netherlands, describes a retrospective study in an academic and a non-academic hospital that merely focuses on the accurateness of the documentation of the withdrawal process rather than on the incidences, motivations

or methods of withdrawal of life-sustaining measures.[3] The first study that shed a light on the issue of the incidence of withdrawal of life-sustaining measures in the Netherlands was our own retrospective study on the use of opioids and sedatives in the general ICU of the Erasmus-MC.[4] In this study we show that the incidence of withdrawal, defined in our protocol as the withdrawing of only ventilation and/or vasoactive medication, is as high as 87 percent in this general academic ICU population. This may seem disproportionately high from a European perspective, however Wunsch and co-authors already reported incidences of active withdrawal of life-sustaining measures even up to 96.1 percent in different hospitals in the UK.[5] In our study on the distribution of the different incidences of withdrawal of life-sustaining measures in the different patient subgroups (chapter 2) we again showed that the overall incidence of withdrawal of life-sustaining measures is high as 83 percent in a mixed academic ICU.[6] Although in our study on the Dutch end-of-life protocol and the level of comfort of the patients (chapter 4) the exact number of withdrawals in comparison with the total number of patients that passed away could not be determined exactly due to a cohort of missed patients, the incidence of withdrawal of life sustaining measures was certainly at least 67 percent. The patient population or case mix can partially explain this high number of withdrawals, however the Dutch attitude towards end-of-life issues certainly also plays an important role. In chapter 4 we describe that the combination of old age and multiple organ failure also explains why inappropriateness of therapy is often mentioned as the key point in the decision process of withdrawing life-sustaining measures. This is in full concurrence with the above-mentioned Dutch values. To understand this, it is very important to note that the Dutch general public is, in contrast with other European countries, strongly against continuing treatment when no cure or improvement is to be expected and that they are, with regard to end-of-life decisions often (even) more progressive than Dutch medical specialists.[7] As we demonstrate in chapter 2, there is a general tendency to more frequent withdrawal of life-sustaining measures in the patient groups with severe neurological damage, independent of the initial cause of the brain damage: traumatic and non-traumatic. Apparently severe brain damage is a general accepted reason for, even early, withdrawal of life-sustaining measures. This is probably due to the fact that a life with possible severe motor and/or mental

impairment is considered an unwanted outcome as judged by both doctors and families and that therefore the risk of stopping too early is outweighed by the risk of continuing treatment with an unfavourable outcome (severe impairment, nursing home dependency and/or a persistent vegetative state) as a result. Severe damage to the brain and thereby damage to the intellectual functioning and the personality of a patient is potentially a more accepted reason for withdrawing of life-sustaining measures than failure of other organ systems. Families in the Netherlands frequently ask their doctor desperately: "Please doctor don't let him become a "vegetable", that is what he certainly never wanted to become".

Geocadin and colleagues analysed already in 2006 the correlation between time to withdrawal of life-sustaining measures and the levels of cortical evoked potentials (CEP) in comatose patients 72 hours after cardiac arrest.[8] They found that 40 of 58 patients (69 percent) died after withdrawal of life sustaining measures, varying from 1 to 25 days after the CEP. By the time that our paper in Neurocritical Care was published in 2012, three other research groups published data that confirmed our observation that the incidence of treatment withdrawal is higher in the patient group with severe brain damage. Moreover two of these studies referred in the discussion section directly, like we did, to the high risk of introducing a withdrawal bias or, in other words, a self-fulfilling prophecy in this vulnerable patient group.[9-11] Although, in the last years, several attempts have been made to improve the process of prognostication for the patient group with severe neurologic damage, the results so far have been disappointing.[12-14] This implies that early withdrawal of life-sustaining measures especially in the young patients with severe brain damage is still an unwanted contribution to the self-fulfilling prophecy of an "inevitable" bad outcome.

OPIOID AND SEDATIVE USE DURING WITHDRAWAL OF LIFE-SUSTAINING MEASURES IN DUTCH ICU'S

Although opioids and sedatives are used and accepted worldwide in general palliative and end-of-life care, there is still a defined reluctance in the use of these medications in the end-of-life care setting in the ICU. This is especially true for Northern America and European countries with an overt Catholic background, like Spain, France, Austria and Italy. The general idea behind this aversion to

opioids or sedatives is that the use of these medications might contribute to an acceleration of the dying process of the patient.
The reaction: "This is about murder" of one of the editors of Intensive Care Medicine to an article about strategies to prevent suffering after various forms of treatment withdrawal on the ICU, is a provocative, but nonetheless strong example of this "belief".[15] In the American medical literature authors often to refer to this presumed dilemma as the "doctrine of double effect".[16] The doubleness consists of the fact that something good, i.e. reaching comfort for the patient, can be accompanied, unwantedly but inevitably, by something bad i.e. the death of the patient. The fact that dosages are indeed relevant in the discussion about palliative care after withdrawal of life-sustaining measures became even clearer when we, during our research, received one of the reviewers' reactions:

"What is the normal therapeutic range if you manage a very sick patient between palliation and euthanasia?"

This remark made not only clear, that dosages and dosage management indeed should be a subject in the end-of-life discussion in the ICU but also that euthanasia should definitely not be a part of it.[17]
In chapter 3 we presented the retrospective data of a patient cohort in which treatment, defined as ventilation and/or vasopressive medication, was withdrawn. We focused on the amount of opioids and sedatives, the severity of disease and the time till death. This was the first time that dosages of opioids and sedatives in end-of-life care setting were described in a population of Dutch ICU-patients. Surprisingly the dosages of both opioids and sedatives reported in our study were generally lower than in most other studies published until then. Although there is of course a publication bias (most likely hospitals with extreme dosages will not easily report this), in contrast to what was expected we used less opioids and sedatives than in the available studies described. The prospective data of the study described in chapter 4, confirm these findings. Also in the non-academic setting the average use of opioids and sedatives is lower than in most published international studies, nevertheless patient comfort was warranted. Although

there is a significant rise in the amount of opioids and sedatives in the last phase of life, the mean dosages remain within the international boundaries of "normal". Key point in the discussion is that the use of opioids and sedatives should always be "goal or effect directed" and never "dosage directed". This goal is in our opinion the comfort of the patient and the perception of this by its relatives and certainly not the acceleration of the dying process. The amount of medication necessary to obtain comfort in a patient may vary widely from patient to patient and may depend on the body weight, the underlying disease, remaining liver and kidney function and certain genetic factors. However, it does not matter what the exact dosage will be, but it does matter that the dosage given is sufficient to reach the desired goal. We conclude that with relatively low dosages of both opioids and sedatives, without compromising ethical values, it is possible to give adequate palliative care in this severely ill and old patient population during withdrawal of life-sustaining measures in the ICU.

This last point about goal directed sedation and pain treatment is elaborated in chapter 5. The editorial presented in chapter 5 is written as a reaction on the proposed end-of-life protocol of the Belgian intensive care society. Although the protocol in itself is accurate and probably well worth using, there was a small line in the protocol that made us worry. The authors of this protocol advocate the introduction and/or increase of medications even in the absence of signs or symptoms in the patient. With this statement they create a very intricate, questionable, and most probably an unethical situation. If neither signs nor symptoms are present then what should guide the titration of the medication, and moreover, what is then the desired treatment goal? We showed that goal directed use of medication does not lead to a quicker death, but what happens if this approach is abandoned? Large increments of both opioids and sedatives or the introduction of barbiturates or even muscle relaxants will certainly lead to hemodynamic instability and suppression of the ventilatory drive, both with death as a definite result. So when signs or symptoms are lacking and if it is certain that death will be the direct result of the action, then it is not palliative care but deliberate termination of life without the request of the patient involved! Some will still call it "euthanasia", but even that is not defendable. Euthanasia is only justified when the patient asked for it beforehand and if the suffering of the patient is evident.

Since these two prerequisites are not met, we can only conclude that this proposal is a call for unethical, unlawful and deliberate termination of life in the ICU.

FACTORS INFLUENCING TIME TILL DEATH

There were three reasons why we wanted to identify the factors that might influence the time till death after withdrawal of life-sustaining measures on the ICU. The most important reason was to be able to predict better how much time it will take for a person to pass away after withdrawal of life-sustaining measures. We know that families are very much interested in this information and that it is stress-reducing for mourning and bereaved families if reliable information can be shared.[18] Reliable information is a significant contributor to family satisfaction on the ICU and that again is an important measure of the quality of ICU care.

On the other hand, it is also useful for logistical reasons to know how long the dying process will take. If you can predict, for example, that the dying process will take more than one day, it can be sensible in the light of scarcity of ICU resources to transfer the patient to a private room on a general ward. The last reason was to eliminate opioids and sedatives as a potential cause of a quicker death in end-of-life care. As already mentioned above the presumed influence of opioids and sedatives on the time till death is still a field of opposing opinions. This is surprising because there is a circumstantial body of evidence with both direct and indirect data from the field of oncology, general palliative care and physiology, that sedatives and opioids do not shorten time till death, but rather prolong the time till death when they are used in a goal directed manner. However in the ICU end-of-life setting there is only one prospective study available that related opioids and sedatives to the time till death. In that single centre study the authors found no correlation.[19] In chapter 4 we present a regression analysis of all the factors that we beforehand considered as contributors to a longer or shorter time till death. We studied the literature and arranged a research meeting on the subject to determine the right predictors. These determinants were used in the regression analysis described in that chapter. As we expected, neither the single maximum dosages nor increments of sedatives did give a statistical significant attribution to a longer time till death in a "enter" regression model. Opioid increments did have a significant effect on the time till death, however in the opposite direction

i.e. contributing to a longer time till death. This was true for both the "enter" as the "stepwise" approach for the regression analysis. Since not all statisticians do accept a stepwise regression analysis we did not use this result for our discussion in the published article. Nevertheless the result of the analysis was obvious: ventilation peak pressure and length of stay are in some models predictors for a quicker time till death after withdrawal of life-sustaining measures and opioids and sedatives are not, or rather prolong the time till death. This is easy to explain, people with severe lung disease or secondary lung damage often need higher peak pressures and FiO2 to get an acceptable level of oxygenation than people who lack lung function problems. When ventilation is withdrawn, the patient will logically de-saturate quicker and subsequently die faster. Length of stay is probably a confounder for something like body energy reserve. The patients with a longer length of stay did clearly not improve under full ICU treatment and therefore treatment was scheduled to be withdrawn. Besides that, they suffered potentially also from all the co-morbidities of a longer stay in the ICU, like decubitus, polyneuropathy, diaphragm wasting, kidney injury and delirium. These factors will logically contribute to an even faster death certainly when several organs are already failing.
Disease severity or organ failure scores like SOFA or Apache II are no statistical significant predictors for the time till death in this Dutch cohort.

Unfortunately, the conclusion that opioids do not shorten time till death is not easily accepted and the doctrine of double effect is still firmly defended by the ones who believe in its "value". Again the comment of one of the reviewers describes perfectly well how deeply rooted this misconception or "moral fiction" is even in the bright light of proof against it:

"The manuscript states: "In our study we show that opioids and sedatives do not give any contribution to shortening of time till death. So if opioids and sedatives do not contribute to shortening of time till death and thereby invalidates the doctrine of double effect, there is no excuse left why a patient should ever suffer from discomfort after withdrawal of life-sustaining measures on the ICU."

"What is the authors' point? Perhaps the problem is lack of English language editing. Or, have they misunderstood the double effect doctrine, which actually supports aggressive use of comfort-directed treatment (including opioids and sedatives), to relieve suffering, even if death is hastened as a secondary effect?"

Despite this kind of comments, we still think that the doctrine of double effect has become indefensible medical nonsense!
An ironical finding, that supports our opinion, is that in the Stanford Encyclopaedia of Philosophy, winter edition 2014, in which all kinds of other philosophical double effect situations are discussed, the opioid double effect is already disqualified as "double", just because there is so much evidence that the arguments for harmfulness of the opioids in the end-of-life setting have been fully undermined.[16]

PATIENT COMFORT BEFORE AND AFTER WITHDRAWAL OF LIFE-SUSTAINING MEASURES

As already explained in the introduction, there is only a limited amount of publications concerning end-of-life care in the ICU. And although there are a few articles on the subject of withdrawal of life-sustaining measures and/or the use of

sedatives and opioids in this setting, in only one article the level of comfort of the patients after withdrawal of life sustaining measures is described.[20] Unfortunately, in this article comfort level and depth of sedation are not objectively measured but estimated by a close family member or other proxy. Surprisingly, there is an on-going discussion about the acceptable levels of opioids and sedatives in end-of-life care while the desired effects of these medications are not at all taken into account in the argumentation. For this reason we prospectively evaluated the effects of the sedatives and opioids by measuring both the level of sedation with two different scales as the level of restlessness as a representative sign for pain or discomfort. Since the patients that are considered candidates for withdrawal of life-sustaining measures are comatose due to the primary disease or are suffering from multiple organ failure and are therefore sedated, objective pain measurement is almost impossible in this population. We also evaluated the incidences of both death rattle and stridor after extubation, as removal of the endotracheal tube is advised in the national Dutch protocol for withdrawal of life-sustaining measures. These signs are rarely a problem for the patient, but can be distressing for both families and health care providers and are therefore to be minimalized when possible. In chapter 5 we describe that the incidences of high scores on the scale of discomfort are relatively low and that most patients are already adequately sedated before the moment of withdrawal of the life-sustaining measures. Another observation we made is that the incidences of death rattle or stridor do not increase despite a significant increase in the number of extubations over the 2 study years.

FAMILY PARTICIPATION IN END-OF-LIFE DECISION-MAKING

In the letter to the editor mentioned in chapter 3-2 we not only discussed the incidence of withdrawal of treatment in Northern Europe, but we also discussed why we think that family participation in the actual withdrawal decision process is an unwanted event. The main argument for this point of view is that it is clear that the family in general has no knowledge or understanding of the medical issues involved and that they are therefore simply not able to make an adequately balanced judgment. Moreover, their opinion will not only be based on the presented medical facts but it will also be formed and influenced by an excess of thoughts

generated by their emotional state of mind. It is generally accepted that making important decisions under severe emotional stress is not a wise thing to do and better to be avoided and this seems for the same reason valid for end-of-life care decisions. The last and most important argument against it is that we know that it is not at all beneficial for the families although they themselves may think the opposite. Azouly and colleagues clearly showed that the risk on posttraumatic stress is directly correlated with the amount of involvement experienced with the decision of withdrawal of life-sustaining measures.[21] In chapter five we show in our result analysis that in the studied non-academic hospitals in only nine percent of the cases fully shared decision-making was mentioned, thereby minimizing the risk of post-traumatic stress in this Dutch ICU patient family population. However further research is necessary to prove if this is truly the case and to analyse what the level of family satisfaction is with this kind of "fully informed, but non co-decision model".

DISEASE PROGRESSION

In chapter 2 as well as in chapter 4, we show that the SOFA scores of the patients in which treatment was withdrawn were significant higher on the last day than on the first in the ICU. Moreover the SOFA scores of these patients were already higher on day 1 than the admission SOFA scores of the average Dutch ICU patient, indicating an already difficult start in the ICU. One should realize that these SOFA scores were calculated afterwards in both studies, so the numbers were not available for the treating physicians at the time of the decision to withdraw life-sustaining measures. Although APACHE scores were developed to make an estimation of what the chance will be for a patient to die in the ICU, the course after the initial admittance is not further corrected in the APACHE-score since it only uses data from the first 24 hours. Interestingly, the SOFA scores show retrospectively, that the patients were admitted already very ill (in concurrence with the high APACHE scores) to the ICU and generally do not improve despite full ICU treatment. On the contrary, the scores deteriorate significantly over time in this group. In this perspective it is logical that in this population the decision to withdraw life-sustaining measures has been discussed. There is no sense in continuing medical treatment that doesn't help to stabilize or improve the condition

of the patient. Although we think that a rising SOFA score under full ICU treatment reflects the failure to reach the aimed ICU treatment goals and therefore makes it defendable to withdraw what isn't working, this opinion is certainly not shared by everyone. Without any counterarguments one of the reviewers simply rebukes our conclusion on this issue:

> *"For example, suggesting that observed increases in severity of illness reflect a failure of ICU care, or justify the decision to withdrawal, contrasts much of what we know about critical care."*

As far as we know there is no literature available evaluating the SOFA scores in the ICU, that supports what this reviewer suggests, on the contrary, the only study that was published relating SOFA scores to treatment withdrawal motivation fully supports our conclusion.[22]

ETHICAL DILEMMAS

Although whether or not to withdraw life-sustaining measures can already be an ethical dilemma in itself, this specific dilemma will not be discussed in this section. In this section three other interesting dilemmas, that are relevant in end-of-life care, will be discussed:

1. *Is it ethically defendable to use the semen of a dead or dying man, without his specific consent, for procreation for the benefit of his wife?*
2. *Is it ethically defendable to ask a patient consent for organ donation after the patient requested termination of ICU treatment?*
3. *Is it ethically defendable to define brain death without the use of the EEG?*

These specific dilemmas are chosen because they proved to be relevant in the daily practice of intensive care medicine, not because of their specific frequent occurrence, but because of the relevance of the underlying themes. These themes, like the value of proxy and patient consent and how to diagnose death are certainly relevant in daily ICU practice. They are also very important because they show us, how personal opinions, ethical rules, medical practices, logic and law all influence our decision-making. They also show us why there is such a high risk on frustration in these cases. When something seems very logical, the law can forbid it for no evident reason. The law may allow something, nevertheless it can be in opposition with a strong held personal opinion. Something can be ethically justified, but may appear very illogical in the given context.
In medical decision-making and certainly in end-of-life care we should always keep the interest of the patient in mind, even though that may cause friction with the family, proxies, fellow colleagues or sometimes even the law.

PERI MORTEM SPERM PROCUREMENT (PMSP), PROCREATION AND THE PROBLEM OF PROXY CONSENT

Chapter 8 is the direct result of a difference in opinion or a difference in point of view between the first and the second author of the article about the right of the woman in the case to get permission for sperm procurement.[23] From a pure ethical perspective it is true that we cannot know if the man in this case would have liked to have children without himself being present (being dead). So therefore it was certainly a sensible decision, with the interest of the patient in mind, not to proceed to sperm procurement in the first place. Although this may be morally justified reasoning it may still sound very illogical in the perspective of proxy consent in end-of-life situations. Organ donation and autopsy are invasive violations of the bodily integrity and therefore definitely not in the interest of the patient, but as a society we accept that these procedures may be done with proxy consent alone, knowing that the decision will be the opposite of the patients wish even in up to 40% of cases.[24] Still we demand for ethical reasons a written consent from a dead or dying man if procreation is the subject. The problem is that we have no idea what the general line of answering would be from men when placed in such

circumstances; there is simply no literature about that. Some ethicists may go therefore for the safe "zero" option: "we don't know if he wanted it, so we suggest not to do it". This is based on the assumption that most men would not want it to happen. However there is another side to it: "which man wouldn't like to comfort his partner or make her a little less sad in a severe and tragic situation (his own dead), and what if PMSP was the last possible act or contribution to achieve that goal?" Would the question then not probably be answered differently?
So this case is illustrative in displaying the friction that is observed more often between ethical reasoning and deductive reasoning. Although they will overlap very often, sometimes they oppose, as in this case and that was one of the reasons why we considered it worth publishing. It is also important to realize that although something can be logically deduced, it still can be in opposition with a personal opinion about right or wrong, as some people will experience is this case.
Another noteworthy lesson from this case is the fact that literally looking over borders might be very helpful in some intricate end-of-life situations. This became also already clear in the brain dead discussion (see below) when we discovered that one could be dead in one country but not yet be dead in another.
But in the PMSP case there arises also a new dilemma. If you, for ethical reasons, have decided not to facilitate sperm procurement, then would you facilitate transport to Belgium on the request of the partner of the patient? The Dutch law may in the end simply forbid PMSP, however it does not forbid transport of a dying or brainstem dead patient to Belgium.

ASKING PERMISSION FOR ORGAN DONATION BEFORE WITHDRAWING LIFE-SUSTAINING MEASURES ON REQUEST OF THE PATIENT

In contrast with chapter 6, where we, inter alia, discuss the value of proxy consent, in this chapter the problem of patient consent in a situation with potentially a conflict of interest between the treating physician and the patient is analysed.
According to Dutch law doctors are allowed to consult the donor registry when death of a patient is imminent. In case of withdrawing life-sustaining- measures on the request of the patient, death is per definition inevitably imminent and therefore the treating physician would be allowed to consult the donor registry. But what is the value of a registry if the patient him/her self is still there and

capable of communicating? The problem is that about 60% of patients is not registered in the donor registry and thereby automatically leave the decision for organ donation to their proxies. We also know that proxies are not very good in knowing or guessing the wishes of their loved ones, they are wrong in up to 40% of cases.[24] Moreover, even if the patient registered his will, he might have changed his mind during his stay in the hospital in several ways, so asking the patient is the most reliable and most ethical way to really get to know what he/she wants after the withdrawal of life-sustaining measures.

Risking the "wrong" answer to the organ donation question is in these cases, in our opinion, less ethically defendable than the theoretical problem of the introduction of competing interests between the patient and the doctor.

THE ROLE OF THE EEG IN DIAGNOSING BRAIN DEATH

In chapter 8 we discuss the role of the EEG in the diagnosis of brain(stem) death. This issue was a direct result of difficulties experienced during the process of gaining family consent for organ donation in patients with severe brain damage.[25] Two problems occurred: firstly it often took several hours after the clinical diagnosis of brainstem death till the EEG could confirm the absence of cortical activity. This was merely a logistical problem, however it was definitely relevant because in some cases families withdrew their consent for organ donation because of the long time waiting. Secondly in some cases the EEG was showing minimal remnant electrical activity in the total absence of all brainstem reflexes and spontaneous respiration (apnoea). In these cases the diagnosis of (whole) brain death had to be postponed and also in these cases some families were inclined to withdraw cooperation with the organ donation process. In some cases the process even had to be converted to a non heart-beating donation because minimal electrical activity persisted even after several EEG's.

As we argued in chapter 8, the EEG does not and cannot actually show what we really want to know and therefore the result of the EEG is more or less an electro-physiological lie that unfortunately some still want to believe in.

In case of absence of all brainstem reflexes and spontaneous respiration, there is no chance of return of consciousness ever and it is certain that all integrative functions of the brainstem and midbrain have ceased to function and thereby

total brain failure is already present; this is independent of residual electrical activity of the motor cortex.
Therefore we argue that the EEG has become irrelevant in the diagnosis of (whole) brain death and that the clinical diagnosis of total brainstem death is more important in the diagnostic pathway towards the right moment of organ donation than the presence of complete cortical silence. The time has come that the Netherlands should synchronise its brain death protocol with other, more practical or rational European countries like for example the UK, this in order to avoid that one can be regarded dead in one country, but not yet dead in the other.

LIMITATIONS, RECOMMENDATIONS AND FUTURE RESEARCH

Although we have concluded that the goal directed use of opioids and sedatives is save in the end-of-life setting, we still need to be careful with generalizing these results. In our study population none of the patients was given remifentanyl or dexmedetomidine. We already know for example that remifentanyl can lead to suppression of the ventilatory drive in already very low dosages and therefore should not be used after withdrawing ventilator support. Dexmedetomidine, a recently introduced sedative, is momentarily only scarcely used in the Netherlands, but it is gaining popularity. At this moment little or no information is available about its effects in end-of-life care. Therefore it remains unclear if with the increasing usage of these drugs the conclusions drawn in this thesis will remain the same. This certainly has to be a subject of future research.

Proxy consent is an important subject in this thesis, however only the practical implications for the presented ethical dilemmas are discussed. As far as we know there is no research available that analyses the attitude of the Dutch population towards this issue. Changing the practice of proxy consent to patient consent alone in organ and tissue donation would have severe implications for the Dutch donation program and is therefore at this moment, without an adequate alternative available, not recommended. The same is valid for the family satisfaction concerning the current end-of-life procedures. We demonstrated that they are practical and efficient, however we have no information about the impact of the Dutch protocol on family members and other proxies. If we want others to believe

that our "no family participation decision model" and the measures taken for good quality end-of-life care are recommendable, we should first prove that Dutch families are indeed satisfied with the current practices.

Intensive care medicine is not only a specialism with many medical and technical challenges, but certainly, as demonstrated by this thesis, also with many ethical challenges. And that is not only valid for the part that we call end-of-life care, but also for the more general care and the ICU research programs, since many decisions in the ICU have important implications for the individual involved and sometimes even directly for the society as a whole. Therefore the more far-reaching decisions need to be evaluated both medically and ethically. The availability of a medical ethicist for an ICU team that works in al large university hospital is therefore a prerequisite and thus highly recommended for comparative hospitals that do not have an ethicist in their team yet.

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10 Summary and conclusions

WITHDRAWAL OF LIFE-SUSTAINING MEASURES

In the Netherlands most patients die in the ICU after a decision to withdraw life-sustaining measures (WOLSM) has been made. The ICU patients in whom life-sustaining measures are withdrawn are relatively old and are severely ill, according to the APACHE and SOFA scores. The patient group with severe trauma to the central nervous system has the highest incidence of WOLSM. Although this seems logical, just because neurological outcome is so difficult to predict, early withdrawing introduces a substantial self-fulfilling prophecy, making reliable prognostication in the near future almost impossible. Especially in the young patient group, even in the case of severe neurological damage, patience is to be advised.

The significant rise in SOFA score in the total patient group can be interpreted as sign that these patients do not seem to benefit medically from ICU treatment; therefore continuation of invasive ICU therapy does not seem to be in proportion in this specific patient group. Sequential organ failure measurements may become helpful in the near future in supporting a clinical decision to withdraw life-sustaining measures.

Most decisions for WOLSM are made in a multidisciplinary setting and are based on the disproportionateness of the treatment. The decision to withdraw life-sustaining measures is a medical decision that is, although communicated with

the families involved, with regard to responsibility not shared with the families because of the proven negative psychological effects.

Opioids and sedatives are widely used and dosages increase significantly during the process of WOLSM in accordance with the need of the patients. Dosages are however comparable with the dose ranges reported in the international medical literature. Moreover they are in our study not a factor contributing to a shorter time till death. The reserve that is still present in the use of these medications by some doctors or nurses, because of the fear of introducing an earlier death, has now proven to be unnecessary. The so-called "doctrine of double effect" has been invalidated. However, introducing new medications or increasing existing medications, when there are no treatable signs or symptoms is ethically reprehensible for that may indeed have an influence on the time till death. In the absence of symptoms after WOLSM introducing or increasing dosages of medications should be considered both unethical as illegal.
Patients in Dutch ICU's die rapidly after WOLSM; the vast majority within 90 minutes, resulting in a dignified death with a low burden of suffering and little signs of discomfort. When the protocol is used properly, there is no rise in the incidence of death rattle and stridor when the ventilator tube is removed more often according to the protocol.

ETHICAL DILEMMAS

Many of the ICU patients are not able to communicate adequately. This is caused by the severity of the disease or because of the necessity of deep sedation. Proxy consent is used very often to validate medical decisions in these cases. Proxy consent is however known not to be representative for the patient in up to 40% of cases. Nevertheless questions concerning treatment choices, end-of-life issues like WOLSM and even autopsy and organ donation may be legally dealt with by a proxy of the patient. In case of peri- or post mortem reproduction, the validity of the proxy consent is valued differently. In this particular case the interest of the patient seems to be better defended than in other situations. Although this may appear illogical, it is ethically defendable. Harvesting and storing of reproductive tissue is in the Netherlands only allowed when there is a written consent of the

patient, proxy consent is not valid. In some cases it might therefore be useful to compare laws and regulations of our neighboring countries to see if there other options are available.

Since proxy consent is not always reliable, it's very important to get to know as quickly as possible the wishes of the patient him/herself. In a patient who is able to communicate that he wants life support to be withdrawn it is essential to get to know what other wishes he has concerning his last moments and the handling of his body afterwards. This also involves the question of organ donation. It is ethically defendable to discuss such issues with an awake patient who deliberately asked for ending of life supporting measures. Not discussing these questions when it is possible is not serving the interest of the patient.

There are two ways of dying in the ICU, by cardiac arrest or by total brain failure characterized as "whole brain dead" when the EEG is flat. From an ethical, practical and physiological point of view it seems illogical to keep on using the concept of whole brain dead. The EEG can provide information about the cortical activity, however when the integrative function of the midbrain and brainstem has totally ceased, cortex activity has become meaningless. It now seems more logical to move on to the concept of brainstem dead, certainly in case of patients who are registered as organ donor, however this has to be well explained to the general public to avoid severe misunderstandings.

11 Samenvatting en conclusies

HET STAKEN VAN DE IC BEHANDELING

In Nederland overlijden de meeste patiënten op de IC na een beslissing om de op genezing gerichte behandeling te staken. De patiëntengroep op de IC waarbij dit gebeurt is relatief oud en over het algemeen zeer ernstig ziek, zoals blijkt uit de APACHE en SOFA scores. De patiëntengroep met ernstige traumata aan het centrale zenuwstelsel heeft de hoogst incidentie van het staken van de op genezing gerichte IC therapie. Hoewel dit misschien wel logisch lijkt, omdat de neurologische prognose zo moeilijk is te voorspellen, introduceert het vroeg onderbreken van de IC behandeling in deze groep juist een "selffulfilling prophecy", waardoor het inschatten van een echte reële prognose ook in de nabije toekomst onmogelijk zal blijken. Zeker in de groep van patiënten met jongere leeftijd met ernstige trauma van het centraal zenuwstelsel moet men terughoudend zijn in het vroeg staken van de IC behandeling.

De significante stijging van de SOFA scores in de gehele patiëntgroep kan gezien worden als een uiting van het feit dat deze groep klaarblijkelijk geen medisch voordeel ondervindt van de IC behandeling; het continueren van de invasieve IC behandeling lijkt daarom in deze groep ook niet meer proportioneel te zijn. De resultaten van het sequentieel vervolgen van orgaan falen parameters, zouden in de nabije toekomst ondersteuning kunnen geven in de besluitvorming om tot het staken van de op genezing gerichte IC therapie te kunnen komen.

De meeste beslissingen om de IC therapie te staken worden in een multidisciplinaire setting genomen en worden gebaseerd op disproportioneel handelen. Het staken van de invasieve IC behandeling is een medische beslissing die bij voorkeur altijd wel wordt uitgelegd aan de betrokken familieleden, maar waar met betrekking tot de besluitvorming, de verantwoordelijkheid voor de beslissing niet met de familie gedeeld wordt vanwege de aangetoonde nadelige psychologische effecten hiervan.

Opiaten en sedativa worden op de IC veelvuldig gebruikt en de doseringen stijgen significant tijdens het onderbreken van de op genezing gerichte therapie, dit in verhouding met de behoefte van de patiënten. De doseringen komen overeen met wat in de internationale literatuur wordt beschreven en de medicatie doseringen zijn in onze studie geen bijdragende factor aan de tijd tot overlijden. De terughoudendheid die nog bij veel dokters en verpleegkundigen bestaat voor het gebruik van deze middelen in verband met de angst de dood te bespoedigen is dus definitief ongegrond gebleken in deze setting. De zogenaamde "dubbel effect leer" is onwaar gebleken. Desalniettemin is het toevoegen van nieuwe medicijnen of het verhogen van doseringen van al lopende medicijnen, op het moment dat er geen behandelbare symptomen zijn, ethisch laakbaar, omdat in die gevallen de medicijnen juist wel een effect op de snelheid van overlijden kunnen hebben. Het geven of ophogen van medicatie in de fase na het onderbreken van de IC behandeling is, bij het ontbreken van symptomen, zowel onethisch als illegaal.

Patiënten overlijden snel op de Nederlandse IC's nadat de op genezing gerichte therapie wordt afgebroken; binnen 90 minuten overlijdt het overgrote deel op een waardige wijze en met een lage lijdenslast zonder veel symptomen van discomfort. Wanneer het onderzochte protocol wordt gebruikt, is er zelfs geen stijging van de incidentie van doodsreutel of stridor aantoonbaar wanneer de beademingsbuis protocollair frequenter verwijderd wordt.

ETHISCHE DILEMMA'S

Aangezien veel IC patiënten of door de ernst van de ziekte of door de noodzaak van diepe sedatie niet in staat zijn normaal te communiceren, wordt er veel gebruik gemaakt van de wettelijke beslissingsbevoegdheid van familieleden in dergelijke omstandigheden om medische beslissingen te kunnen nemen. Uit onderzoek is echter gebleken dat in 40% van de gevallen de beslissing van de familie helaas niet strookt met de wens van de patiënt zelf. Desondanks mogen in situaties rondom het levenseinde beslissingen over medische behandelingskeuze, orgaan donatie en/of obductie legaal door familie of een partner genomen worden. In het geval van een wens tot voortplanting rondom het levenseinde wordt het toestemmingsrecht van de familie of partner in de praktijk toch een andere waarde toegekend. In dit soort omstandigheden lijkt het belang van de patiënt zwaarder gewogen te worden. Hoewel dit onlogisch kan klinken is het wel degelijk ethisch verdedigbaar. Het afnemen en bewaren van geslachtelijk weefsel met als doel voortplanting is in Nederland dan ook alleen toegestaan wanneer daarover een schriftelijke verklaring van de patiënt zelf beschikbaar is, de partner of naaste familie hebben daarin geen toestemmingsrecht. In sommige gevallen kan het nuttig zijn om naar de wet- en regelgeving in ons omringende landen te kijken om te zien of daar nog wel mogelijkheden open liggen.

Aangezien de mening van de familie niet altijd betrouwbaar is, is het dus des te meer van belang de wil van de patiënt zelf te weten te komen. Als een patiënt in staat is op betrouwbare wijze aan te geven dat hij niet wil dat zijn levensondersteunende IC therapie wordt voortgezet, is het van essentieel belang om ook zijn andere wensen rondom het levenseinde en de omgang met zijn lichaam daarna te weten te komen. Hier hoort vanzelfsprekend dan ook de orgaandonatie vraag bij. Het is ethisch zeer goed te verdedigen dat dit gesprek met een wakkere patiënt, die zelf om het staken van de levensondersteunende therapie heeft gevraagd, wordt gevoerd. Het niet voeren van een dergelijk gesprek gaat namelijk juist tegen het adequaat behartigen van de belangen van de patiënt in.

Er zijn op de IC twee manieren om te overlijden; door hartstilstand en door volledig hersenfalen, wat als "(volledig) hersendood" gedefinieerd wordt en waarbij het

vlakke EEG uiteindelijk bepalend is voor de uitslag. Vanuit een ethisch, praktisch en fysiologisch perspectief is het onlogisch om nog langer het concept van volledige hersendood te blijven gebruiken. Het EEG kan wel enige informatie leveren over nog aanwezige corticale activiteit, echter wanneer de integratieve functie van lagere hersendelen en/of de hersenstam volledig is verdwenen, is restactiviteit van de cortex betekenisloos geworden. In dat perspectief zou het logischer zijn om met het concept hersenstamdood te gaan werken, zeker bij patiënten die als orgaandonor geregistreerd staan, maar dit moet dan wel op een overtuigende wijze aan het publiek worden uitgelegd om ernstige misverstanden te voorkomen.

SECTION IV

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PHD PORTFOLIO

International conferences		accreditation points
17-03-2015	Brussels Belgium, Annual ISICEM congress 2015	24
27-09-2014	Barcelona Spain, Annual Congress ESICM 2014	30
05-10-2013	Paris France, Annual Congress ESICM 2013	30
13-10-2012	Lisbon Portugal, Annual Congress ESICM 2012	30
01-10-2011	Berlin Germany, Annual Congress ESICM 2011	30
10-10-2010	Barcelona Spain, Annual Congress ESICM 2010	30
24-03-2009	Brussels Belgium, Annual ISICEM congress 2009	24
12-01-2009	Villars Swiss, 7e Winter Workshop Intensive Care	25

National conferences		
23-04-2014	Maastricht, 26e Internistendagen 2014	14
06-02-2014	De Bosch, NVIC Nederlandse Intensivistendagen 2014	10
13-02-2013	Ede, NVIC Nederlandse Intensivistendagen 2013	18
25-04-2012	Maastricht, Internistendagen 2012	15
08-02-2012	Ede, NVIC Nederlandse Intensivistendagen 2012	18
23-06-2011	Rotterdam, Erasmus Critical Care Days	12
13-04-2011	Maastricht, Internistendagen 2011	14
09-02-2011	Ede, NVIC Nederlandse Intensivistendagen 2011	17
22-04-2010	Maastricht, Internistendagen 2010	12
19-11-2009	Ede, NVIC Infectiedagen 2009	1

Other educational sessions		
31-03-2015	Goes, Donorzorg het begint bij de herkenning	2
04-12-2014	Utrecht, Landelijke discussiebijeenkomst NICE 2014	4
20-11-2014	Rotterdam Bijeenkomst intensivisten en neurologen	2
04-12-2013	Utrecht, Landelijke discussiebijeenkomst NICE 2013	4
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07-12-2010	E-learning CME British Medical Journal	1
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Courses	
19-01-2015	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers
15-06-2011	Utrecht, Training MDS en KIIC volgens NICE/NVIC/NVICV
30-09-2011	Utrecht, Basis Cursus SPSS, Eduvision

Teaching	
2009-2015	Minoren onderwijs “Shock” en “Nierfalen”
2009-2015	Introductie cursus IC “NICE”, “Familie communicatie” en “Transport van de IC patient”
2009-2015	Bed-side teaching fellow’s co-assistenten en minoren
2012-2015	Onderwijsmaand IC “Ethiek, Communicatie en Orgaandonatie”

LIST OF PUBLICATIONS AND PRESENTATIONS

INTERNATIONAL PUBLICATIONS

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16 mei 2011, Maastricht, NVA dagen: "Staken van de behandeling op de IC, hoe, wie, wat en wanneer?"

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8 februari 2012 Ede, NVIC dagen: "Drugs for mechanical ventilation withdrawal".

8 juni 2012 Utrecht, Venticare: "Wanneer is medische behandeling nog zinvol?"

11 oktober 2012, Gorinchem, Schakels in de zorg: "Wanneer is medische behandeling nog zinvol?" en "Sedativa en opioiden gebruik bij het staken van IC behandeling".

16 oktober 2012, Lisbon, ESCIM annual congress: "Opioids and sedatives do not seem to contribute to time till death after withdrawal of life sustaining therapy in Dutch critically ill ICU patients".

10 januari 2013, Rotterdam, Thema avond "Medische besluitvorming rondom het levenseinde", Maasstad Ziekenhuis: "Zinloos versus zinvol".

4 april 2013, Vlissingen, Palliatieve Netwerk Zeeland, conferentie "Rondom het Levenseinde": "Goal directed" gebruik van sedativa en morfine leidt niet tot een sneller overlijden bij kritiek zieke IC patiënten waarbij de behandeling wordt gestaakt.

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5 juni 2015, Utrecht, Venticare, "Wanneer wordt het palliatief" en "End-of-life".

PUBLIC MEDIA

Article in "Scanner" December 2013, concerning the ethical dilemma's in post mortem sperma procurement on the ICU

Television interview for "De vijfde dag" concerning the timing and potential difficulties in asking bereaved families for organ donation. http://www.eo.nl/ditisdedag/reportage/item/video-wanneer-vraag-je-om-organen/

Interview in newspaper "Trouw" 13-2-2015, "Als de familie nee zegt", about problems in getting family consent when asking for organ donation

Letter to newspaper NRC 12-03-2015, a short reaction on an opinion article against organ donation

CURRICULUM VITAE

Jelle Leendert Epker was born on the eighth of December 1972 in Dordrecht the Netherlands. In the spring of 1991 he finished his secondary school (VWO, Thuredrecht College, Dordrecht). A few months later he was accepted for the medical studies at the Erasmus University in Rotterdam. He obtained his medical degree "cum laude" in January 1998. The next year Jelle Epker married with Marion Dik in Leiden. His first medical work was as a resident (ANIOS) in the "IJsselland Ziekenhuis" in Capelle aan den IJssel, where he, after 2 years, was nominated for the specialty training in internal medicine at the Erasmus Medical University. In the last months of 2005 he started working on the intensive care as the last stage of his internal medicine speciality training. He applied for a fellowship "intensive care medicine" deliberately in the only academic hospital without an approved IC fellowship. In 2007 he was asked to join the medical staff of the Erasmus-MC department of adult intensive care medicine. That same year the fellowship was finally officially approved and in 2009 he obtained as one of the first doctors the title of "Intensive Care Specialist" in Rotterdam. During the last months of his fellowship, he agreed on starting a PhD study on end-of-life issues in the intensive care. Until the publication of this thesis he has been a staff member of the intensive care department of the Erasmus MC with a special interest in end-of-life care, medical ethical dilemmas, family communication and neurological infectious diseases.

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De allereerste ideeën voor dit proefschrift dateren waarschijnlijk nog uit de periode dat ik nog maar net internist was en officieel dus nog niet eens fellow voor de intensive care. De ideeën kregen vastere vormen eind 2008 en in 2009 werd mij het voorstel gedaan om te proberen er een promotie van te maken oftewel "er uiteindelijk een nietje doorheen te slaan". En dat is nu inmiddels zowel letterlijk als figuurlijk gebeurd. Zonder de steun en hulp van anderen had ik het niet voor elkaar gekregen en daarom dan ook dit welgemeende dankwoord.

Beste Jan allereerst wil ik jou bedanken. Het is voor mij een eer dat ik je via dit dankwoord in mijn proefschrift persoonlijk mag en kan bedanken. Ik ben je namelijk om meerdere redenen oprecht veel dank verschuldigd. Niet alleen ben je drijvende kracht geweest achter de vorming van de afdeling IC Volwassenen zoals we die nu kennen, waardoor de voor mij als "wanne be" fellow toen zo vurig begeerde IC opleiding uiteindelijk kon worden binnengehaald, maar ook omdat ik op jouw uitnodiging deel mocht gaan uitmaken van de net geformeerde IC staf van diezelfde afdeling. Als opleider heb je toen zeer duidelijk het nut van onderzoek en onderwijs laten zien en mede door jouw belangstelling in de ethische aspecten van het klinisch handelen op de IC heeft Erwin als mijn co-promotor de ruimte gekregen zijn onderzoeken op te zetten en ideeën uit te werken. Binnen diezelfde ruimte kreeg ik van jou via Erwin opnieuw een uitnodiging om een stap

verder te zetten in mijn carrière en dit proefschrift is het eindresultaat van dat traject. Je kamerdeur stond altijd open en je nam altijd de tijd om de kleine en grote vragen te beantwoorden. Ik heb enorm veel van je kunnen leren op diverse fronten: ik weet nu hoe je moet "doorpakken", hoe je zaken "gecontroleerd uit de hand kan laten lopen" en ik weet wanneer "hij 'm niet meer gaat worden". Allemaal essentieel om een goede intensivist en onderzoeker te kunnen zijn. Jan bedankt dat jij mijn opleider en promotor hebt willen zijn. Ik ben benieuwd wat de Rotterdam - New York connectie voor ons beiden in de toekomst zal opleveren.

Beste Erwin, jij hebt mij al in 2007 voorzichtig gepolst voor onderzoek in de "end-of-life" richting. Je was op zoek naar een dokter die wel zin had in onderzoek en ook iets had met ethiek en mogelijk ook verstand had van sedativa en opiaten. Ik wist toen nog niet zo goed wat ik van jou als ethicus en van het voorstel tot promotie onderzoek moest denken. Gelukkig is me dat wel duidelijk geworden en kan je nu zelf beoordelen wat er van is gekomen, "dat dan weer wel". Gelukkig was mijn koudwatervrees van korte duur, en bleken we veel meer gemeenschappelijk te hebben dan ik in eerste instantie vermoed had: een voorliefde voor absurde humor zoals in "The Far Side", vakanties op de Azoren, de Mac, oude medische boeken en medische geschiedenis in het algemeen. Recent ontdekten we ook nog eens dat we dezelfde soort muziek weten te waarderen. Verder hebben we regelmatig samen de conclusie moeten trekken dat er een situatie "voor gevorderden" was ontstaan op onze afdeling en de beschouwingen met jou daarover waren altijd meer dan de moeite waard. Die ene keer dat ik het echt volstrekt met je oneens was heb je mij gestimuleerd mijn overwegingen aan het papier toe te vertrouwen als "goede ethische vingeroefening". Juist die vingeroefening is uiteindelijk zelfs een apart hoofdstuk in dit proefschrift geworden. Ik wil je van harte bedanken voor de prettige en ontspannen samenwerking en de humor waarmee jij de zaken in het leven benadert (zelfs ook mijn promotietraject) en de altijd accurate en zeer snelle reactie op de aan jou toegestuurde papers. Erwin, nogmaals bedankt dat jij mijn co-promotor wilde zijn en ik verheug me op het vooruitzicht van continuering van onze "journalistieke" samenwerking in de "emo" research.

Mijn dank gaat vanzelfsprekend zeker ook uit naar professor de Beaufort, professor Girbes en professor Huygen die als leden van de kleine commissie bereid waren dit proefschrift, dat op de grens van ethiek, palliatieve zorg en IC geneeskunde balanceert op haar merites te beoordelen. Hartelijk dank voor jullie snelle respons en de nuttige suggesties en verbeteringen. Professor de Beaufort, u wil ik graag speciaal bedanken dat u ondanks uw zeer drukke werkzaamheden zo aan het eind van het studiejaar toch de taak van commissie secretaris op u wilde nemen.

Beste Martin en Mariël, promoveren zonder paranimfen is feitelijk onmogelijk en ik prijs me dan ook gelukkig met paranimfen zoals jullie. Onze vriendschap heeft diepe wortels en zelfs in 1999 hadden jullie allebei ook al een rol bij een ander prachtig life-event. Jullie hebben in de afgelopen jaren allebei altijd veel belangstelling getoond voor mijn onderzoek en de nieuwste ontwikkelingen daarin. Het is dan ook kenmerkend voor jullie dat geen van jullie beiden er enig moment over hoefde na te denken om ja te zeggen op de vraag of jullie paranimf wilden zijn. Ik ben blij dat jullie als theoloog en een psycholoog zowel letterlijk als figuurlijk achter me willen staan Bedankt voor jullie vriendschap, de geweldige support en het vertrouwen dat jullie ook in mij stellen.

Zonder de diverse collega's in het Ikazia en Haga ziekenhuis zou hoofdstuk 4 nooit tot stand zijn gekomen. Hoewel indirect vele mensen aan de STOPIC studie hebben bijgedragen wil ik met name Jeannette Schoonderbeek, Michael Franken en Piet Melief bedanken voor het feit dat ik het vertrouwen kreeg om deze studie bij hen op de IC te mogen uitvoeren. Zonder de inspanningen van de research verpleegkundigen en dan met name Lettie van de Berg en Hanneke van Emden zouden de data nooit zo compleet en overzichtelijk aangeleverd zijn geweest. Ik wil jullie bij dezen bedanken voor jullie enthousiasme voor de studie en de geweldige medewerking die ik altijd van jullie heb gekregen voor, tijdens en ook nog ver nadat de studie was afgelopen!

Zoverre ze nog niet hierboven genoemd zijn, ben ik natuurlijk ook veel dank verschuldigd aan mijn mede auteurs. Martijn, bedankt dat je als fellow zo voortvarend met het stuk bestemd voor Neurocritical Care aan de slag bent gegaan.

Je bent welverdiend eerste auteur geworden, je hebt er hard voor gewerkt. Maar eerlijk is eerlijk, zonder de data die door Mariska al waren verzameld en de eerste draft die zij heeft aangeleverd was het allemaal niet zo snel gegaan. Mathieu, bedankt voor je adviezen ten behoeve van ons stuk over de diagnostiek van de hersendood. Jouw onderbouwde neurologische inbreng is essentieel geweest en ik ben er trots op dat ik met jou dit stuk in het NTvG heb kunnen publiceren. Hetzelfde geldt natuurlijk ook voor prof Wijdicks, beste Eelco, zonder jouw bijdrage aan ons manuscript, zou het waarschijnlijk nooit de impact hebben gekregen die het nu heeft gehad. Beste Hester, zelden heb ik zo'n ontspannen en gezellige statisticus ontmoet. Je hebt me, ondanks je eigen drukke bestaan, enorm geholpen met je statistische adviezen en zeker ook met je goedkeurende en bemoedigende opmerkingen over wat ik zelf allemaal al aan SPSS bewerkingen had gedaan. Ook je slimme antwoorden op de lastige vragen van de kritische reviewers zijn goud waard geweest, bedankt! Yorick, we zaten een tijdlang in het zelfde "emo" schuitje en dat was een aangename ervaring. Wij hebben veel gelachen en met name ons verblijf in Berlijn is om diverse redenen memorabel geworden. Het was mooi en goed om elkaar met papers en abstracts voor congressen te kunnen helpen. Ik ben er trots op dat wij ons allebei straks zowel dr. als Intensivist zullen mogen noemen, zij het dat wij dat ten opzichte van elkaar in omgekeerde volgorde zullen bereiken.

Beste Claudette, toen er voor de zoveelste keer een reviewer kritiek uitte op de Engelse grammatica van het artikel bestemd voor A&A, was ik opgelucht dat ik als vriend een beroep op jou als Canadian "native speaker" kon doen. Je hebt met veel enthousiasme de artikelteksten gecorrigeerd en mij geholpen de Engelse spelling en grammatica beter te beheersen. Mede door jouw hulp is het stuk uiteindelijk dan ook geaccepteerd voor publicatie. Met de vertaling van het Nederlandse NTvG stuk naar het Engels, heb je mij veel kostbare uren kunnen besparen, nogmaals veel dank daarvoor. Inmiddels heb je zelf van de nood een deugd gemaakt door je eigen vertaalbureautje op te zetten. Ik kan jou uit eigen ervaring daarom van harte bij iedereen aanbevelen.
Beste Ralf, het was een obscure "go no go" opdracht voor jou, waar je initieel niet goed uit kwam, die ons uiteindelijk op een goede avond echt bij elkaar bracht. Het resulteerde voor jou in je eigen Camino de Santiago met Marleen,

"best holiday ever" en je diploma van de St. Joost academie. Je aanbod daarna om de vormgeving van mijn proefschrift voor je rekening te willen nemen kwam als een geschenk uit de hemel. Jij hebt met de prachtige vormgeving mijn proefschrift naar een hoger niveau getild. Het was me een waar genoegen om samen met jou de ontwerpen langs te lopen, muziek te luisteren, een beetje te filosoferen en gaandeweg te ontdekken dat jouw ontwerpen perfect aansloten bij wat ik initieel voor ogen had.

Beste collega's van de afdeling Intensive Care Volwassenen, verpleging, mede intensivisten, assistenten en fellows. Ik wil jullie heel hartelijk bedanken voor jullie support en geduld van de afgelopen jaren. Promoveren is een langdurig proces, dat niet altijd over rozen gaat. Sommigen van jullie hebben bemoedigende woorden gesproken, anderen hebben diensten opgevangen en weer anderen wisten met oprechte en goed getimede belangstelling en humor me weer opnieuw te motiveren en een gevallen draad weer op te pakken. Hoewel ik niemand tekort wil doen, wil ik toch speciaal (en deels natuurlijk ook als pars pro totem) mijn "fellow" fellow van het begin en mijn huidige bureaumaatje Hilde bedanken. Samen begonnen we in 2006 aan een IC opleiding die er eigenlijk niet was en allebei hebben we sindsdien (met niet te vergeten Jasper) gewoon volgehouden. Ik denk nog altijd met veel plezier terug naar onze tijd op de box op 3 zuid waar we (samen met Tim en Yorick) allebei de eerste stappen op het pad der wetenschap zetten. Omdat wij samen grotendeels gelijktijdig in hetzelfde traject hebben gezeten, hebben we veel lief en leed gedeeld. Jouw enorme doorzettingsvermogen en kalmte in diverse gecompliceerde en lastige situaties is een groot voorbeeld voor mij geweest. Bedankt ook dat je al jouw ervaringen met het promotietraject zo laagdrempelig met mij hebt willen delen, ik heb daar veel profijt van gehad.

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gedaan. In onze vriendschap zijn we op hoge toppen geweest en daar zagen we de arenden vliegen maar we zijn evenzo door diepe dalen gegaan. Dank voor je trouwe vriendschap, je geduld, je bemoedigende woorden en natuurlijk je spontane creativiteit. Maar vooral bedankt dat je in het "kringgesprek" altijd naar me hebt willen luisteren.

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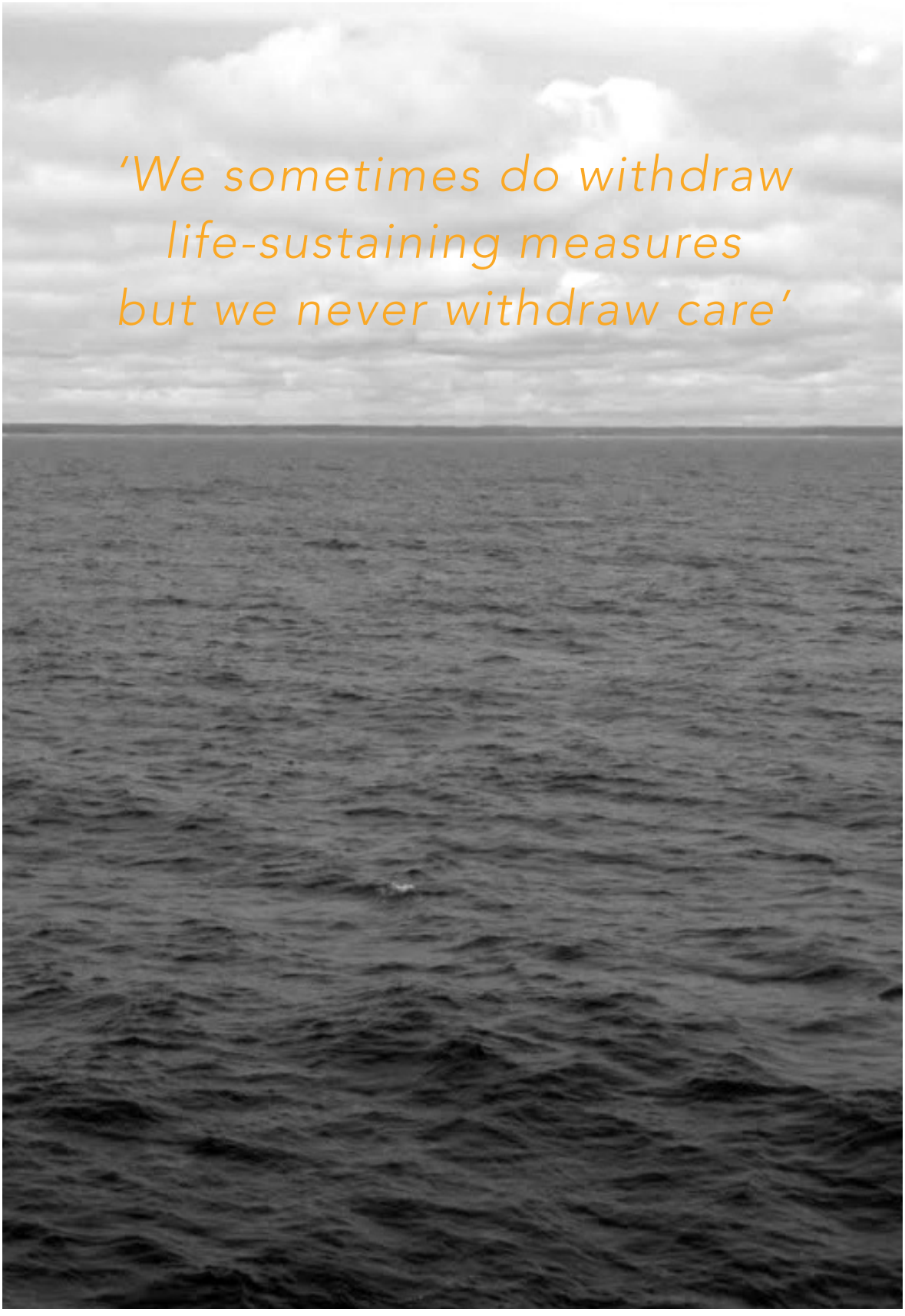
Lieve Pa en Ma, bij ons thuis werd nieuwsgierigheid altijd al als een gezonde eigenschap gekwalificeerd en bij de vele interessante discussies die we vroeger thuis hadden, leerden jullie ons al dat het vooral en bovenal om de kracht van het argument moet gaan en niet om de emoties er omheen. Ook hebben jullie mij en Harry altijd aangemoedigd om verder te leren als daar de mogelijkheid toe was. Mede door die veilige en stevige basis heb ik mijn opleidingen en ook deze promotie goed af kunnen ronden. Bedankt dat jullie met heel veel liefde en belangstelling de degelijke fundamenten hebben gelegd waarop ik verder heb kunnen bouwen.

Lieve Marion, je staat niet graag in de spotlights en je vindt dat een dankwoord niet meer zou moeten zijn dan een welgemeend "dank je wel". Ik zal daarom hier geen opsomming geven van al die dingen waarom ik je zo waardeer en waar ik je allemaal dankbaar voor ben. Jij krijgt van mij dus gewoon een oprecht en welgemeend "dank je wel voor alles", omdat ik weet, dat jij weet, wat dat uiteindelijk allemaal voor mij betekent. Lieve Marion, bedankt voor alles!


'We sometimes do withdraw
life-sustaining measures
but we never withdraw care'